THE CHICAGO MEDICAL SCHOOL
QUARTERLY

CONTENTS

•

TOXIC HEPATITIS

MELVIN R. SALK, M.D.*

Introduction

As the result of observations over a period of four years, some of us have come to regard toxic hepatitis associated with renal damage as a not uncommon clinical entity. It is a disease of relatively constant form and pathology but of varied etiology. To the best of our knowledge, the disease concept to be presented is not widely noted in the literature nor generally accepted. The term, "toxic," may be an unfortunate one but is used, for the present, to differentiate this form of combined liver and renal disease (not the so-called hepatorenal syndrome as usually described) from other types of medical jaundice due to virus infection or associated with cirrhosis. Hemolytic jaundices present no differential diagnostic problem. Furthermore, toxic hepatitis is associated with, or initiated by, a variety of infectious states. The clinical picture, the blood chemistries, and the pathology of this disease complex (regardless of etiology) resemble that of liver disease classically ascribed to known toxins and poisons. Therefore, because of these similarities and the preceding reasons, the use of "toxic hepatitis" (usually associated with renal dam-

age) as a diagnostic designation enjoys at least temporary local validity.

This presentation makes no pretense of absolute completeness or final authority but is an attempt to survey the field, convey impressions derived from experience and to stimulate interest.

Etiology

The numerous causes of Toxic Hepatitis may be partially classified and listed as follows:

Drugs and Poisons
  Cinchophen
  Sulfonamide preparations
  Arsenic preparations
  Lead preparations
  Carbon tetrachloride, benzene, trinitrotoluene, and other industrial solvents
  Chloroform
  Phosphorus
  Alcohol
Bacterial and Parasitic
  Pneumonia (all types)
  Septicemia (all types)
  Peritonitis
  Severe local sepsis with systemic reaction
  Severe urosepsis
  Amebiasis
  Spirochaetosis
    Weil's disease
    Canicola fever
    Bovine leptospirosis
    Swineherd's disease
  Plasmodial (malaria - Blackwater fever)
Metabolic and Degenerative
  Thyrotoxicosis
  Diabetes mellitus
  Chronic ulcerative colitis

---

* Department of Medicine, The Chicago Medical School.

Generalized psoriasis
Dermatomyositis
Lupus erythematosus
Rheumatoid arthritis
Severe avitaminosis and starvation
Miscellaneous
Idiopathic
Yellow fever
Anoxemia
Some toxemias of pregnancy

With reference to certain items in the preceding categories, there are some observations to be made. Whether or not sulfonamide preparations cause liver damage is still a matter of debate. We are inclined to consider them potentially and occasionally hepatotoxic. Lead preparations similarly are suspect. We have observed a case of chronic (industrial) lead poisoning with hepatitis for more than a year. Arsenic is undoubtedly hepatotoxic but, in light of present knowledge, many of the cases in the literature of past years were probably homologous serum hepatitis ("syringe hepatitis"). Alcohol, particularly in severe acute intoxications associated with little or no food intake, is a frequent offender. Toxic hepatitis (mild to severe) can be diagnosed in a large percentage of cases of pneumonia if the possibility is investigated.

In hyperthyroidism, liver damage with or without jaundice should be looked for in every instance. One of the first cases seen by us, in this connection, had previously been diagnosed as carcinoma of the head of the pancreas. Wherever metabolic duress is severe or prolonged, as is frequently the situation in diabetes mellitus (as well as hyperthyroid disease), liver damage is quite possible, often in the form of toxic hepatitis. With regard to the remainder of states listed under Metabolic and Degenerative disorders, we have observed liver (and some renal) involvement in all of them ranging from simple fatty liver to fatty toxic hepatitis to fully developed Laennec cirrhosis.

Up to the present time, a fair number of the cases seen are still relegated to the Idiopathic group. In some, the only common etiologic denominator has been an occupation in the meat or poultry industries (Weil's disease? Canicola fever? Bovine Leptospirosis? Swineherd's disease?). In a general way, anoxemia, whatever the cause (e.g., severe anemia,

passive congestion from cardiac disease, carbon monoxide poisoning), may produce the toxic hepatitis picture. Yellow fever, although viral in origin, is included because, in many respects, it resembles the toxic hepatitides. We have had no actual experience with this latter disease.

Epidemiology

It can be stated, almost categorically, that this disease is not transmissable, that is, from man to man, or insect or animal to man, except in a very few instances, namely:

Weil's Disease—contamination of food and drink by infected rat droppings and urine.

Canicola Fever—contamination of food and drink by infected dog (and possibly cat) droppings and urine.

Bovine Leptospirosis—handling of infected cattle or the partaking of their products.

Swineherd's Disease—handling of infected swine or the partaking of their products.

Amoebic Hepatitis — secondary to amoebiasis contracted by ingestion of contaminated (directly or indirectly by man) food or drink.

Blackwater Fever—presumably malarial (P. falciparum via Anopheles mosquito) and precipitated by fatigue, chilling, alcoholism and quinine.

Yellow Fever — bite of infected Aedes Egypti mosquito.

Idiopathic Group—not immediately determinable one way or another.

More evidence of the general non-transmissibility of "toxic hepatitis" can be drawn from the work of some of Eppinger's group in Vienna many years ago. Over a long period of time, they had available large numbers of jaundiced patients diagnosed variously as catarrhal jaundice, cirrhosis, or surgical jaundice. The blood of these patients was injected into a large group of "volunteers" and, in no instance (reported) were they able to reproduce jaundice—this in contradistinction to Neefe's excellent work (experimental production of viral hepatitis in humans) of relatively recent date. We must assume, with no more information

available, that by coincidence none of the Viennese "donors" had viral hepatitis and that probably many of them (those with catarrhal jaundice and possibly some with supposed surgical jaundice) had toxic hepatitis.

Contributing Factors

Age—a variable item—having no definite significance except in the idiopathic group where the incidence appeared to be greater past the age of 35.

Sex—Although not statistically evaluated, we have seen most cases among males. This preponderance may well be more apparent than real.

Race — no particular preponderance in any one direction.

Nutrition — here, as with cirrhosis, malnutrition (perforce associated with subvitaminosis) is a very important contributory factor. This is generally accepted for all forms of liver disease.

Stress—this is food for thought, particularly interesting in view of Hans Selye's contentions. Reperusal of the agents listed under *Etiology* will reveal many items which do not primarily involve the liver and kidneys, yet these organs, during the progress of the particular disease process or insult, eventually become involved producing the picture of toxic hepatitis with renal damage. Could it not be said that disease processes were forms of stress? Could not the toxic hepatitis complex, as described in this article, be in at least some of the instances a "disease of adaptation"?

Character of the Disease

It is our opinion that the term "hepatorenal syndrome" is frequently inadequately or improperly defined, and that it is either not the proper term to use or that the usual implications may be incorrect. The usual implications (or mechanisms) are (1) that the liver, sustaining a severe insult either from specific disease or surgical trauma (direct or indirect), loses some of its ability to handle metabolites and noxious or toxic substances and that part of this "detoxifying burden" then falls upon the kidneys which in turn, subjected to these substances, become

diseased or, (2) that the liver, sorely damaged (from whatever the cause), releases toxic tissue break-down products and bile pigments which, in passing through the kidneys, cause damage.

We have, however, seen viral hepatitides, desperately ill with severe liver damage and intense jaundice, rarely showing appreciable renal damage. Yet, at autopsy, in the fatal cases, the kidneys were as heavily bile-stained as in the toxic hepatitis cases and, in many instances, the gross and microscopic liver damage was much greater. Whatever the inciting agency, we feel that both the liver and the kidneys are probably affected independently and approximately simultaneously. It is not the province of this paper to enlarge upon this matter which will be the main subject of a future publication (Jaundice and Azotemia).

The following discussion is of general character. It should be understood that all points will not be applicable to every case and that all cases will not embody all of the characteristics. This is no more nor less true than for any other disease. Clinically, the single outstanding and most consistent finding is that all cases are exceedingly ill ("toxic") when first seen.

Usually the history and findings of the initiating or predisposing disease, or the story of medication, poisoning, or intoxication are elicited. Where none of the preceding is obtainable or engrafted upon the picture, the following story of onset (typical of the "idiopathic" group) is more or less characteristic. Onset is usually quite sudden, with little or no prodrome. G.I. symptoms (anorexia, nausea and vomiting) predominate. Abdominal cramps and diarrhea are not infrequent. Profound weakness and malaise are common complaints. Generalized muscular cramping, particularly of the calf muscles (no special significance yet deduced), is frequent and often times the only presenting complaint. Chilliness to severe rigors sometimes occurs. Almost invariably there is a complaint of fever—101° F. or much higher (fever in this range is not common in viral hepatitis). Jaundice of eyes and skin, and darken-

ing of the urine appear rapidly after the onset of symptoms. Pruritus and pale stools are not too infrequently noted. Oliguria is variable. Headache is not uncommon.

On physical examination, the patient is very sick and sometimes delirious or semi-comatose. The jaundice has an orange hue — usually (though not invariably) deep. Fetor hepaticus is variable, depending upon the severity of the hepatic damage (particularly to de-aminizing functions). Spider naevi are rarely found unless there is underlying chronic hepatitis or cirrhosis. Adenopathy is not characteristically found, whereas it is quite common in viral hepatitis. The liver is anywhere from 1 to 7 or 8 fingers below the right costal margin in the mid-clavicular line and tenderness is variable, while the spleen is palpably enlarged in about 50% of all cases and is usually not tender. Ascites and edema are not seen unless there is associated cirrhosis with portal hypertension and/or severe plasma albumin reduction.

Laboratory Findings

1. Urine — usually dark, heavily laden with bile pigments. Urobilinogen may be 4+ or, at the height of the disease, present only in traces or none at all— this "obstruction" (intra-hepatic obstruction) may persist anywhere from 1 day to 4 weeks or longer. The specific gravity is within normal range unless antecedent renal disease is present. A 2+ to 4+ albuminuria is almost always seen at the height of the disease; occasionally granular and hyalin casts with a few cells are seen.

2. Stools—frequently pale tan to clay color.

3. Cephalin Cholesterol Flocculation — zero in about 50% of cases seen. The presumable explanation is the absence of increased periportal infiltration (white cells), a situation which is common in surgical jaundice produced by Drugs and Toxins and in the Idiopathic Group. Where a significantly positive test does occur (uncomplicated by cirrhosis) it remains so for only a short time (as compared to the almost reluctant reversal to normal seen in other hepatic jaun-

dices). Furthermore, a globulin alteration must occur to make this and other similar tests positive — thus, since globulin is presumably elaborated (normal forms and otherwise) by the reticulo-endothelial system, including WBC's, and since this system is not particularly involved in a large number of toxic hepatitis cases, these tests will tend to be normal.

4. Thymol Turbidity—usually at pathological level (that is, above 4 units) but very seldom above 12 units. Here, an alteration in phospholipids is involved (in addition to the globulin factor) and is usually prominent enough to give an abnormal test even though globulin is unaltered or only slightly so.

5. Sedimentation Rate — almost invariably high. This, with a low (though above 4, usually) thymol turbidity is a very common combination almost peculiar to toxic hepatitis.

6. NPN — almost always significantly elevated (depending, of course, upon two variables — the degree of renal damage and/or the depression of hepatic deaminizing function). We have seen several cases with levels of 200 to 300 mgm.% or better, with equivalent creatinine levels.

7. Total Protein — usually somewhat diminished and, occasionally, markedly so.

8. A/G Ratio—most frequently below 1.5, and not uncommonly inverted (below 1.0). This depreciation is usually at the expense of plasma albumin, for seldom is a rise in plasma globulin noted.

9. Total Cholesterol—in most cases, elevated above 250 mgm.%— though not invariably so. Commonly it is highest during obstructed periods. Where the level is unusually low (and this is occasionally seen in any of the various types of jaundice), there is no adequate explanation.

10. Cholesterol Esters — frequently depressed (below 60%). This is a very sensitive test for liver damage.

11. Alkaline Phosphatase—excluding all other causes (non-hepatic) for elevation (and with obvious liver disease

and jaundice present)— the plasma level is almost always elevated, quite frequently to levels of 15 to 25 B.U., and occasionally higher.

12. Total Serum Bilirubin — generally quite high, with levels of 20, 30, or even 40 mgm.% not uncommon.

13. Prothrombin Activity — usually decreased (that is, prothrombin concentration is diminished). Response to Vitamin K is present, but is much slower than in surgical jaundice.

14. Plasma Ions—(Ca, Na, P, Cl) and CO_2 combining power—ordinarily in keeping with the degree of azotemia.

15. Urea Clearance—usually depressed.

16. Bromsulfalein, Hippuric Acid, and Galactose tolerance tests will all show damage.

17. WBC—usually a moderate leukocytosis with high percentage of polymorphonuclear cells.

18. Na/Cl Excretion Ratio (Urinary) — will, in many cases, at the height of the disease, be depressed considerably below 1.0 (this is also seen in viral hepatitis and in cirrhosis with jaundice) but, as recovery progresses, the ratio returns to normal.

19. Zinc Sulphate Turbidity (Kunkel) — no personal experience with this test. It is supposed, however, to have a high diagnostic specificity in distinguishing between medical and surgical jaundice.

20. Specific agglutinations are available for all aforementioned leptospiral infections. Injection of blood or urine from suspected cases intraperitoneally into guinea pigs may aid in establishing the diagnosis.

Differential Diagnosis

There may occasionally be some difficulty in distinguishing toxic hepatitis from choledocholithiasis. Intermittancy of icterus and urinary obstruction is not characteristic of hepatitis. Rarely is the condition confused with jaundices produced by malignancies. The risk of exploratory surgery is great and the mortality is high in individuals past the age of 50 with toxic hepatitis. If reasonable doubt exists after thorough investigation, liver biopsy should be done.

Pathology

It can be said that the liver exhibits generalized damage, most frequently (but not invariably) concentrated in the central areas, with moderate to heavy fatty changes, minimal to mild periportal infiltrations (except where associated with infection), and not infrequent bile thrombi. The kidneys are bile-stained and show damage to the entire nephron.

Course and Treatment

The course initially is frequently quite rugged. If recovery occurs (fortunately, in most cases it does), the duration of illness is generally shorter than in the average case of viral hepatitis.

The therapy involves the two cardinal principles of absolute bed-rest and adequate diet.

Bed-rest until all chemistries are normal (this is the optimum situation) and clinical cure is apparent; then a week's trial of household (limited) activity, and a recheck of complaints (if any), physical examination and chemistries.

Diet—regardless of appetite, a minimum of 300 gms. of sugar (or the equivalent thereof) daily by whatever practical route. Proteins—when orally taken, at least 150 gms. daily. Intravenous amino acids, if oral diet cannot be taken, are of value (60 to 120 gms. daily) even if much is wasted. Fat—under 90 gms. initially and then slowly increased to tolerance. Full vitamin supplementation—to supply at least these amounts daily: 25 mgm. B_1, 100 mgm. Nicotinic Acid, 200 to 500 mgm. Vitamin C, 20,000 to 40,000 U Vitamin A, and 10 to 20 concentrated yeast tablets (Burroughs-Wellcome is a convenient preparation). Specific lipotropic agents may be used; also Intraheptol, Crude Liver, B-complex preparations, and therapeutic formula vitamin capsules.

Where the initiating agency (drugs, poisons, infection) is known, specific measures (e.g., BAL, anti-biotics, etc.) are used in addition to the above.

In our experience, no specific therapy for the azotemia has ever been required.

Summary

An attempt has been made to present a concept of "toxic hepatitis" which may be clinically useful. The idea of this

disease, when attributed to an obvious poison or toxin, is not new. However, when applied over as wide a field as described in the preceding pages, the concept to date, largely holds only local recognition and acceptance. If no more than interest and curiosity have been stimulated, this article has served its purpose.

BIBLIOGRAPHY

Wilensky, A. O.: "Relation of nitrogen bodies of blood to surgical problems in liver and in biliary tract disease." Archives of Surgery, *14*: 1222-44, June, 1927.

Rabinowitch, I. M.: "Biochemical findings in a rare case of acute yellow atrophy of liver with particular reference to origin of urea in body." J. Biol. Chem., *83*: 333-35, August, 1929.

Helwig, F. C. and Schutz, C. B.: "A further contribution to the liver-kidney syndrome." J. Lab. and Clin. Med., *21*: 264, 1935.

Lichtman, S. S. and Sohval, A. R.: "Clinical disorders with associated hepatic and renal manifestations, with especial reference to the so-called hepatorenal syndrome." Am. J. Digest. Diseases and Nutrition, *4*: 26-32, March, 1937.

Garlock, J. H. and Klein, S. H.: "So-called hepatorenal syndrome." Annals of Surg., *107*: 82-95, January, 1938.

Meyer, K. A., Popper, H. and Steigmann, F.: "Significance of rise of non-protein nitrogen in medical and surgical jaundice." J.A.M.A., *117*: 847-50, September 6, 1941.

Bernkopf, H., Olitzki, L. and Stuczynski, L. A.: "Studies on bovine and human leptospirosis." J. Inf. Diseases, *80, 1*: 53-63, 1947.

Fopper, H. and Franklin, M.: "Diagnosis of hepatitis by histologic and functional laboratory methods. J. A. M. A., *137*, 3: 230-34, May 15, 1948.

Franklin, M., Salk, M. R., Steigmann, F. and Popper H.: "Clinical, functional and histologic responses of fatty metamorphosis of human liver to lipotropic therapy." Am. J. of Clin. Path., *18:* 4, April, 1948.

Popper, H. and Steigmann, F.: "Differential diagnosis between medical and surgical jaundice by laboratory tests." Annals of Int. Med., *19*, 3: 469-87, September, 1948.

Sandler, R.: "The disease of swineherds in Israel." Harefu'ah, December, 1949.

Himsworth, H. P.: "The Liver and Its Diseases." Harvard Univ. Press, 1948.

Salk, M. R. and Todd, W. H.: "Jaundice and azotemia." In manuscript.

Todd, W. H. and Salk, M. R.: "The cephalin cholesterol flocculation test in the diagnosis of jaundice." Unpublished, 1946.

Salk, M. R. and Narut, L. F.: "Clinical studies in the differential diagnosis of jaundice." Unpublished, 1947.

Narut, L. F. and Salk, M. R.: "A mathematical approach to the diagnosis of jaundice using a battery of laboratory tests." Unpublished, 1947.

TREATMENT OF PSYCHIATRIC EMERGENCIES

H. H. GARNER, M.D.*

In the treatment of psychiatric emergencies, the same basic concepts hold true as for treatment in general of the psychiatric patient. Symptoms are an expression of:

(1) Previously inhibited impulses, drives, tendencies, attitudes and behavior which on coming to expression are experienced as something alien to the usual mode of behavior (ego alien tendencies).

(2) Attempts at control by defensive measures previously utilized or new defensive measures.

(3) Loss of function expressed either as a defect in the integrative functioning of the individual or through release

symptoms which are represented by (1) above.

When the symptoms produced are overwhelming as a result of the acuteness or the severity of the disturbing influences which precipitated the illness, we may consider the individual as suffering from a psychiatric emergency. It would be too extensive a task to include every emergency situation in the scope of this article. The following are some of those commonly encountered and are particularly of significance to the general practitioner who may first be confronted with such emergencies.

Suicidal Attempts

Suicidal attempts, especially by barbiturates, are among the most common psychiatric emergencies with which one

* Professor and Chairman, Department of Neurology and Psychiatry, The Chicago Medical School.

must deal. The need to take such action as is necessary in dealing with the inhalation of gases, ingestion of chemicals such as iodine, arsenic and others is self evident. In the treatment of barbiturate intoxication the routine measures for stomach and intestinal evacuation are carried out, fluids are administered either as glucose or saline or other fluid solutions aimed at maintaining the fluid and chemical equilibrium of the body. Analeptic drugs are available to combat the depressant action of the drugs used in suicidal attempts. The following are among those in frequent use:

(1) Picrotoxin, although one of the most commonly used analeptics, has the disadvantage of being more slowly destroyed than some of the others. Convulsions may occur as the patient is recovering. It is given intravenously in doses of 2-4 cc repeated at frequent intervals until corneal reflexes return and the patient shows evidence of being aroused.

(2) Metrazol given as a 10% solution is preferable in my opinion. It may be administered through the tubing of the intravenous fluid in 4 to 10cc for the first dose depending upon the depth of the coma and the amount of drug taken. This dose is repeated in five to fifteen minute intervals or less until evidence of the patient's response to the medication is present.

(3) Benzedrine sulphate and other amphetamines can be used much in the same manner as picrotoxin and metrazol and may be alternated with them or be given simultaneously.

(4) Other stimulants which may be used in the absence of those mentioned above are: whiskey—30cc at intervals if the patient is awake enough to swallow; aromatic spirits of ammonia—2 to 4cc may likewise be given; caffeine sodium benzoate—.32 gms. to 1 gm. given intramuscularly; strychnine sulphate—.003 to .006 gms. intramuscularly.

Severe Depression

Every severe depression is a psychiatric emergency in that suicide is an ever present danger. Whenever there is any doubt about the possibility of suicide, immediate hospitalization where proper precautionary measures can be taken is imperative. Where such measures are not carried out the patient should be given frequent appointments and stress placed on the fact that the patient is expected to keep the appointment. The physician must assume a protective non-condemning role and the patient made to feel that the doctor has a personal interest in his welfare. Electro shock treatment may be given as an outpatient treatment when hospitalization cannot be accomplished. Electro shock treatment considerably decreases the risk of suicide but should be supported by frequent contacts with the patient for psychotherapy (reassurance, alleviation of guilt feelings, improving self-esteem).

Excited States

The acutely disturbed patient as seen in catatonic excitement, combative and destructive behavior as an expression of release of previously inhibited impulses, manic excitement, homosexual panic states, in the course of acute alcoholism and the delirium of intoxication and infection is a psychiatric emergency. All other diseases in which the integrative functions of the individual are so disturbed that reality testing and the adaptive functioning of the individual are disorganized, fragmented and distorted in terms of acute disturbances in behavior should be included.

Treatment of such patients is divisible into two groupings:

(1) Treatment which is more or less similar for all excitement states and is directed at maintaining a degree of chemical and physiological equilibrium in the individual so as to prevent a severe homeostatic unbalance which in some cases may lead to death.

(a) From 2000 to 3000cc of fluids should be given daily as glucose in such fluid media as Hartmans or Ringers solution. When the disturbed state is of short duration a glucose saline solution may be adequate.

(b) Small doses of insulin, enough to cover the glucose administered seems to have a beneficial effect in the metabolism of the sugar given.

(c) Adequate multivitamin therapy for nutritional needs is supplied by the standard multiple vitamin preparations given

once or twice daily. Where gastritis is present, as in the alcoholic, the use of injectable vitamins is desirable.

(d) When the disturbance is prolonged and when the replacement through intravenous, subcutaneous and intra-muscular therapy routes cannot be considered adequate, the use of nasal tube feedings in which eggnog mixtures containing supplementary vitamins is desirable. 500 to 750cc of eggnog mixture may be given at a feeding and this may be repeated one or more times daily.

(e) The use of medication to suppress behavior based on disturbed integrative functioning of the individual must be directed at giving a sufficient quantity of the drug to either interfere with the consciousness of the individual or suppress unacceptable behavioral tendencies. In most instances therapy will have the social aim of producing a sufficient degree of unconsciousness so that the patient can be managed without danger to himself or others. The drugs most commonly used and their approximate dosage are tabulated (Table 1). Many other barbiturate products are used. It is best to become acquainted with the action of a few and utilize those with which one is most familiar. To mention a few there are: tuinal, seconal, ipral, dial, butisol sodium, and phenobarbital.

patient in the pack so that all motor movements of body and the extremities are completely inhibited. Such a pack can be made from a large sized bed sheet by wringing it out in tepid water. This pack will have both sedative effect and protective value for the patient and others. Precautions against accidental injury are always in order. The room should be darkened, visitors minimized, loud noises and other stimuli avoided to decrease the reactive behavior of the patient to environmental stimuli.

(2) Treatment which is intended to be specific or especially applicable to certain diseases or syndromes in which the acutely disturbed behavior represented but a phase of the illness.

Neurosyphilis. Treatment should be started as soon as the diagnosis has been made. If the patient's hospitalization cannot be immediately effected and the diagnosis is established, 300,000 units of penicillin may be given daily during the period of treatment of the acute disturbance. If the patient is in a hospital, fever therapy with typhoid should be started.

Acute Alcoholism, Delirium tremens, Alcoholic acute hallucinosis. Treatment which is considered desirable includes glucose for improved carbohydrate metabolism with insulin to cover the glucose.

Table 1

DRUG	ORAL	INTRAV.	INTRAM.	PER RECTUM
Sodium Amytal	.2-.6 gm.	.2-1 gm.	.2-1 gm.	.4-1 gm.
Nembutal	.1-.3 gm.	up to 1 gm. very slowly	.5-1 gm.	.2-1 gm.
Paraldehyde	8-16 cc	4-8 cc very slowly		12-20 cc in olive oil retention enema
Chloral hydrate Bromide Mixture	1-2 gms. of each			2 gms. as retention enema

In some instances the use of suppressive methods by means of drugs may be undesirable or medication may not be immediately available. A wet sheet pack can be used as effective restraint and sedation by properly wrapping the

(a) 10% glucose in saline
(b) 50% glucose administered without dilution.

Tolserol (Squibb) and other similar drugs are found to decrease the anxiety and tremor of the acute alcoholism or de-

lirium occurring in the course of chronic alcoholism. It may be given by mouth in .5gm. to 1gm. doses four times daily.

Delirium tremons requires some precautionary measures and treatment of a special nature. Because of the fever and debilitation which are frequently present, the use of restraints should be minimized and wet packs used only for very short periods and under extremely careful supervision. Paraldehyde in 12 to 16cc (3 to 4 drachm) doses is the preferred hypnotic. Fluids should be increased to an intake of 3000 to 4000cc unless cardiac complications contraindicate their use. Caloric intake with suitable types of food should be at a high level. Three to four thousand calories daily with supplementary vitamins—Vitamin B Complex including nicotinic acid —should be given by subcutaneous route because of the poor gastric and intestinal absorption of the alcoholic. Insulin in UX to XV three times daily enhances carbohydrate metabolism.

Meningitides and similar states require specific treatment with the antibiotics. Such supportive treatment being utilized for the nutritional disbalance and suppressive treatment for excitement as is indicated.

Bromide delirium requires less consideration than it did when bromide medication was more commonly used. A blood bromide of 150mgm. or more per 100cc suggests the possibility of a bromide delirium. The treatment with chloride which replaces the bromide ion is specific. Chlorides may be given by subcutaneous, intravenous or oral routes. Liquids should be forced and therapy for delirium states administered.

Traumatizing Experiences

In a sense, every person subjected to traumatizing experiences in which a serious threat to the physical well-being of the individual is felt can be considered as being a psychiatric emergency. Traumatic experiences are especially disorganizing and disabling when the injury can be anticipated yet the possibility for escape blocked either because of external factors or internal frustrations against escape such as guilt and shame. The organism is flooded with excitement

that cannot be mastered through activity or bound effectively leading to a state of anxiety with disorganized, erratic and uneconomic behavior. Such traumatic neuroses may be considered emergency psychiatric problems in that immediate and intensive treatment directed at alleviating the psychologic disorder is required. All physicians engaged in industrial work should be concerned with prophylactic measures which will minimize the frequency and severity of traumatic neuroses and physicians in general have a similar responsibility with regard to emotional states produced as a result of accident.

The aim of the physician should be to create an atmosphere of assurance and rest following the injury. All the resources to make the environment a safe and secure place should be utilized. A maternal nurse-like attitude on the part of the physician with an interest in the details of the comfort of the patient with regard to sleep, warmth, food and other personal needs is required. Careful questioning about the incidents occurring at the time of the accident will help to prevent amnesic reactions which may become dissociated. A kind, reassuring attitude must be maintained by the physician while the accident situation is recounted and a careful appraisal of the patient's ability to deal with the anxiety created is important. The patient should not be pushed to a point beyond his ability to manage the anxiety created by the review of the traumatic incident. In some instances barbiturates, sodium amytal .6gm. (2-3gr. capsules), tuinal, seconal, nembutal, ipral or other agents may be utilized to maintain a period of sleep of from 24 to 48 hours. During the period between sleep and incomplete awakening the patient is fed and toilet needs are met. At the same time some abreaction of the traumatic incident may be accomplished with the aid afforded by the suppression of the anxiety by the barbiturates. Questioning should always be such as to avoid suggestive symptom-giving since the dependent, sometimes helpless, position of the patient makes him more prone to accept symptoms offered by the physician as something he should have.

Epileptic States

Epileptic manifestations of an acute character which may be considered emergency in nature include status epilepticus and epileptic furors.

Status epilepticus, a state of continuous seizure patterns, requires such therapeutic procedures as will suppress the irritable discharging motor cortex. In the administration of the drugs previously mentioned for states of disturbed activity, the intravenous route is desirable if it can be used. When the intravenous barbiturates are not available, paraldehyde may be given directly from the container since it is self-sterilizing. It should be given slowly and cautiously since it produces considerable pulmonary irritation.

Epileptic furors constitute an emergency problem which requires prompt action on the part of the physician to prevent serious injury to others or the patient. The therapeutic necessity is to suppress the patient's consciousness and motor activity so that he may be managed with safety. This can be accomplished by:

(a) Use of suppressive drugs as for status epilepticus.

(b) The conversion of the psychological pattern of discharge into a discharge which is primarily physiological by use of convulsant agents. Metrazol in 3 to 5cc doses may be injected intravenously very rapidly to produce a convulsion followed by a sleep which can then be maintained by oral or intramuscular hypnotics. When available an electro shock convulsion may be substituted for that induced by analeptic drugs.

Hypoglycemic States

Hypoglycemic states may appear in the course of diabetic management, as a result of pancreatic tumors, or disturbed endocrine function (pituitary). The disordered mental condition, when recognized as having its origin in a hypoglycemic state, should be treated by intravenous glucose 50cc of a 25 or 50% solution. This is usually sufficient to remove the symptoms. Treatment for the etiologic factors responsible must of necessity follow.

I must emphasize that treatment of the psychiatric emergency is frequently treatment directed at suppression of behavioral tendencies which are likely to be injurious to the patient or socially unacceptable. In another sphere, the treatment is directed at restoring such physiological disbalance as occurs in infections, traumatic degenerative, nutritional and metabolic, toxic and vascular disturbances while at the same time applying the principles involved in suppression of disturbed and disorganized behavior. The treatment of the patient should, during this phase of the illness and following the control of the emergency state, take into account the total personality needs of the individual and such long term treatment procedures as will improve the patient's ability to withstand inner and outer stresses should be instituted as soon as possible.

BIBLIOGRAPHY

Fenichel, Otto—The Psychoanalytic Theory of the Neurosis. W. W. Norton & Co. 1945.

Beckman, Harry—Treatment in General Practice: W. B. Saunders & Co.

Noyes, Arthur P.—Modern Clinical Psychiatry: W. B. Saunders & Co., '48.

Goldstein, H. H. et al: Induced Hyperinsulinism: Ill. Med. Journ. 73, 147-151 (1938).

Goldstein, H. H., Weinberg, Jack—Experimental Evidence of the Anticonvulsant Properties of Sodium Diphenyl Hydantoinate: Arch. Neurol. & Psych., 43, 454-455 (1940).

Kardiner, Abram—The Traumatic Neuroses of War: Psychosomatic Monograph II, III (1941).

THE HYALURONIDASE-HYALURONIC ACID SYSTEM

DONALD H. ATLAS, M.D., Ph.D.,* and SEYMOUR LEVINE, M.D.**

Since 1928 when Duran-Reynals found that certain extracts known as spreading factors greatly increased the infectivity of vaccine virus upon intradermal injection in rabbits, a vast amount of information has been produced on this subject. These spreading factors are believed to be mycolytic enzymes which act by the breakdown of integral components of the matrix or ground substance. Recently, most workers have been concerned with the enzyme *hyaluronidase,* which specifically hydrolizes one of the basic components of the ground substance known as hyaluronic acid.

Hyaluronic acid is a long chain, non-antigenic mucopolysaccharide consisting of equimolar combination of glucuronic acid and N-Acetylglucosamine of high molecular weight, the solutions of which are consequently extremely viscous.

During the hydrolysis by hyaluronidase, the polysaccharide is first depolymerized and then hydrolized, thereby changing the reaction characteristics of the intact polymer. The altered characteristics of the hyaluronic acid such as the property of forming a turbid sol with protein, clot formation, and viscosity of solution are used to assay the activity of the enzyme. Thus, the spreading activity of hyaluronidase is due to the removal of tissue barrier to fluid diffusion by inactivating the hyaluronic gel present in the ground substance of the connective tissues.

Hyaluronidase has been isolated from numerous bacteria and from a large variety of organs and tissues, including certain neoplasms. It may also be found in testicular extracts and some snake venoms. It may be implicated in such diverse biological phenomena as fertilization of the ovum, the pathological chemistry of rheumatoid arthritis, and the pathogenesis of rheumatic fever.

The clinical application of hyaluronidase has lagged far behind our scientific knowledge of this substance and has been somewhat disappointing. It is efficacious in microgram amounts in facilitating the rapid absorption of subcutaneous fluid preparations, such as physiological saline and albumin solutions. It is the purpose of this article to discuss the relationship of the hyaluronic acid-hyaluronidase system to various disease processes.

The effect of hyaluronidase on hyaluronic acid may be of key significance in the mechanism of fertilization. The ovum is surrounded by a cloud of cumulative cells and intracellular matrix which contains hyaluronic acid. Hyaluronidase causes these cumulus cells to spread, leaving the ovum somewhat denuded, thus enabling the sperm to penetrate and complete the process of fertilization. However, the use of hyaluronidase clinically in sterility cases has not been effective.

Hyaluronidase has been successfully used to increase the diffusion of local anesthetic agents, and produces a higher percentage of successful nerve blocks in other types of infiltration anesthesia. That this effect is specifically on the ground substance and not due to vasodilating effects is proved by the fact that when epinephrine is added to a mixture of hyaluronidase with a local anesthetic agent, epinephrine actually increases the spreading effect.

Although the effect of the enzyme is primarily on the ground substance of the connective tissue, recently it has been shown that the enzyme may increase the permeability of mucous membranes. It has been shown that the absorption of penicillin through the nasal mucous membrane is enhanced by the concurrent local administration of hyaluronidase. Since chilling enhances the effect of the enzyme, perhaps by the inhibitory effect of cold on anti-hyaluronidase substances, we have a possible explanation for the increased incidence of virus respiratory infections during inclement weather.

Altschuler and Angevine have shown that the essential feature of fibrinoid

---

* Assistant Professor of Medicine, The Chicago Medical School.
** Class of 1947, The Chicago Medical School.

formation, which has recently been incriminated as the basic lesion in a variety of conditions, especially Lupus Erythematosus Disseminata, is the precipitation of the hyaluronic acid in the ground substance. The pathogenesis of this precipitation is under investigation at present and may be due either to alterations in pH or hyaluronidase activity.

In vitro and in vivo animal experiments, indicate that hyaluronic acid by virtue of its high viscosity increases the sedimentation rate, and conversely, hyaluronidase decreases it.

In the rarely occurring pretibial myxedema it has been shown by Watson and Pearce that this myxedematous tissue contains increased amounts of hyaluronic acid. The clinical application of this fact is that these lesions can be dissolved by infiltration with the enzyme.

Meyer has found that pathological synovial fluids as obtained from patients with rheumatoid arthritis contain excessive amounts of hyaluronic acid, but paradoxically, also have a lower viscosity. From this he has inferred that in this disease the synovial cells may produce excessive amounts of hyaluronic acid which, in turn, stimulates the outpouring of hyaluronidase.

By far, the most important consideration of this subject is the relationship to rheumatic fever. This enzyme system has been implicated in rheumatic fever as a result of four observations, i.e., (1) hyaluronic acid is an important constituent of connective tissue, the seat of the rheumatic process; (2) hemolytic streptococci produce hyaluronic acid and hyaluronidase; (3) hyaluronidase has been reported by Guerra and others to produce in the skin of rheumatic patients spreading reactions which may be inhibited by salicylates; (4) the relationship of this enzyme and the acid to the sedimentation rate.

The relationships of various strains of streptococci to rheumatic fever and the mechanisms of this relationship have been the subject of extensive controversy and a voluminous literature. Probably the best summary of this confusing material is the monograph of Waksman. It seems in spite of the widespread agree-

ment that streptococcal infections precipitate rheumatic attacks, no one type of streptococcus has been successfully incriminated. A direct infectious cause of the Aschoff nodule, allergic mechanisms, individual susceptibility, metabolic, and dietary factors has never been fully clarified to the satisfaction of most authorities in this field. Hyaluronic acid has been isolated from skin, synovial fluid, mesenchymal tumors, vitreous humor, and umbilical cord. Its presence in connective tissue has been established only by indirect evidence, such as the spreading activity of hyaluronidase and the presence of metachromatic material throughout the connective tissue, which has staining reactions of each of the mucopolysaccharides (hyaluronic acid and chondroitin sulphuric acid). If this staining reaction is abolished by treating tissue with hyaluronidase before the stain is applied, one may conjecture that the staining material is hyaluronic acid. However, the same effect of testicular hyaluronidase on chondroitin sulphuric acid has been observed which indicates that staining reactions are not specific for hyaluronic acid. The production of hyaluronidase by streptococci is again insufficient evidence that this enzyme is related to rheumatic fever.

Hemolytic streptococci that produce the largest amounts of hyaluronidase are usually unencapsulated, whereas, the types of streptococci that have been most frequently incriminated in rheumatic exacerbations are usually encapsulated and do not produce extensive amounts of hyaluronidase. Certain types of streptococci which produce the enzyme as well as the acid have not been implicated in the disease.

The picture is further complicated by the isolation of antihyaluronidase substances previously mentioned. Different inhibitors have been isolated for testicular and streptococcal hyaluronidase. The inhibitor of heat-labile testicular hyaluronidase has been isolated from the albumin fraction of human serum while the inhibitor for streptococcal hyaluronidase resides among the Gamma globulins. The term "anti-invasion" has been given to some of these substances. These inhibit-

ors have been found to be increased in the sera of patients with rheumatic fever and other infections. Dorfman has theorized that a streptococcal infection releases increased amounts of hyaluronic acid in the connective tissue, thereby stimulating the production of hyaluronidase which, in turn, calls for a defense reaction by antihyaluronidase substances. This theory is supported by finding an increased amount of antistreptococcal hyaluronidase in rheumatic fever.

Our interest in this subject was stimulated by the papers of Guerra, who reported unusual susceptibility in rheumatic fever subjects as indicated by massive reactions to the intradermal wheals of hyaluronidase—Evans blue solutions. He further reported that these unusually massive spreading reactions were inhibited by salicylates. If Guerra's report could be substantiated, a skin test for early rheumatic fever was conceivable. However, investigation of this problem in our laboratory and by others has not substantiated Guerra's observation. We were unable to demonstrate that the patient with rheumatic fever showed either greater or lesser resistance to the spreading factor by the skin test method. Dorfman, however, has corroborated the inhibitory effect of salicylates on spreading reactions in the experimental animal. Our own experiments along these lines also confirm the fact that in some individuals, salicylates retard spreading reactions, and thus give information as to the mechanism of the therapeutic effects of this drug. It should be noted, however, that in some normal individuals, no such inhibitory effects by salicylates were observed. This means that other factors — perhaps antihyaluronidase substances — may vary considerably in normal individuals. Further work along these lines is in progress in our laboratory.

No discussion of rheumatic fever and its therapy is complete without a consideration of the newest developments in ACTH and Cortisone. Dramatic therapeutic effects have been reported in the treatment of acute rheumatic fever with these substances, but as yet, the mechanism of this therapeutic reaction has eluded investigators.

Whether these newest "miracle drugs" perform by reducing the "hyperergic" reactivity of cells or in some way protect the ground substance from the effects of the rheumatic process remains for future investigators to elucidate.

One must await impatiently the rich yields that will certainly be forthcoming from these investigative mines.

BIBLIOGRAPHY

1. Altschuler, C. H., and Angevine, D. M.: Histo-chemical Studies on the Pathogenesis of Fibrinoid. Am. J. Path., 25: 1061, No. 5, 1949.
2. Dorfman, A., Reimers, E. J., and Ott, M. L.: Action of Sodium Salicylate on Hyaluronidase. Proc. Soc. Exp. Bio. & Med., 64, 337, 1947.
3. Guerra, F.: Hyaluronidase Inhibition by Sodium Salicylate in Rheumatic Fever. Science, 103: 686, 1946.
4. Guerra, F.: Action of Sodium Salicylate and Sulafadiazin on Hyaluronidase. J. Pharm. and Exp. Therapeutics, 87: 193, 1946.
5. Haas, E.: On the Mechanism of Invasion. J. Bio. Chem., 163, 63, 1946.
6. Harris, T. N., and Friedman, S.: Relation of the Hemolytic Streptococcus to Rheumatic Fever. Effect of Streptococci spreading factor in rheumatic patients and others. Amer. J. Dis. Children, 77: 561, 1949.
7. Hechter, O., Dopkeen, S. K., and Yudell, M. H.: The clinical use of Hyaluronidase in Hypodermoclysis. J. of Ped., 30, 645, No. 6, 1947.
8. Kirby, C. K., Eckenhoff, J. E., and Looby, J. P.: The use of hyaluronidase with local anesthetic agents in nerve block and infiltration anesthesia. Surgery, 25, 101, No. 1, 1949.
9. Meyer, K.: The Biological significance of Hyaluronic Acid and Hyaluronidase. Physio. Review, 27: 335, 1947.
10. Waksman, B. H.: The Etiology of Rheumatic Fever: a review of theories and evidence. Med., 28, No. 2, 1949.
11. Watson, E. M., and Pearce, R. H.: The Mucopolysaccharide content of the skin in localized pretibial myxedema. II. Amer. J. Clin. Path., 19: No. 5, 1949.

BRONCHIAL ASTHMA

A. L. AARONSON, M.D.*

In this treatise, I propose to combine lectures given on the subject with some of the more recent advances, as obtained from the literature, so that the student will have a composite picture of the disease.

Definition

The name "Asthma" was first used by Hippocrates in 406-377 B.C., and implied "hurried breathing" or "I gasp for breath." A more complete definition has more recently been given by Glaser, in which he says, "Bronchial Asthma is a form of obstructive emphysema of allergic origin, involving both lungs throughout; characterized by paroxysmal attacks of dyspnea, chiefly expiratory; accompanied by wheezing heard on auscultation of the chest; and typically relieved, at least in the early stages of an attack, by sympathomimetic drugs." Simply stated, bronchial asthma may be described as a disease characterized by coughing, wheezing, and dyspnea, which in severe form may become orthopnea.

Historical

Hippocrates first used the term "asthma" to indicate certain types or degrees of breathlessness. Celsus, in the first century A.D., distinguished the mild form of the disease, dyspnea, as differentiated from the more severe form, orthopnea. Aretaeus, a contemporary of Celsus, described "breathlessness following running or laborious work" as asthma. Galen (130-201 A.D.) proposed two causes for the disease, namely, "thick or pituitous humors" and "a crude tubercle in the lungs."

Van Helmont (1577-1644), was the first to recognize and introduce the concept of a "nervous" or "spasmodic asthma," characterized by sudden "epileptic-like" attacks. Sir John Floyer in 1698 published "A Treatise of the Asthma," stating minute symptoms with marked accuracy, since he himself suffered from asthma.

* Assistant Professor of Medicine, The Chicago Medical School.

Cullen in 1784 attempted to present spasmodic or convulsive asthma as a clinical entity, and believed it due to constriction of the bronchial muscles.

It was with Laennec's (1819) development of improved methods of auscultation, that new fields of endeavor were opened for more accurate studies of asthma. He was able to differentiate between cardiac and pulmonary lesions, and made the oft repeated statement that "shortness of breath is but a symptom which may be due to many causes." Salter (1860) recognized the difference between cardiac and spasmodic asthma, and was the first to indicate the association with animal emanations, and to emphasize the importance of hereditary factors. Leyden in 1872 described small, oblong, octahedral crystals found in the sputum, and Curschmann in 1882 noted spirals in the sputum, and believed them to be the causative factor in attacks.

Etiology

The causes of bronchial asthma are almost as varied as the patients who suffer from this ailment. Its frequency and distribution is variably quoted by the authors as occurring in 0.05 to 3 percent of the population. So far as age is concerned, about one-third of all asthmatics date the beginning to the first decade of life; another 50% begin between the ages of 10 and 40 years. Thereafter the incidence diminishes, being low after the age 60 years. Inheritance is a major factor, a positive family history being obtained in about 60% of most reported series, although some authors quote as high as 75 to 80% in their reports. It must be remembered that not infrequently the child may reveal evidence of allergic disease even before the parent.

Sex seems to play a minor role in asthma, since males make up 53 to 54% of all asthmatics. Prior to puberty males predominate 3 to 1; from puberty to the menopause, females lead in a 5 to 4 ratio; after 50 years of age males again lead by 5 to 4. So far as race is con-

cerned, the percentage is highly in favor of the white man, although there has been an increasing incidence among the American Negro. Asthma is rarely found in Eskimos and Indians. Social status seems to be relatively unimportant, since there is no difference in occurrence in the poor or affluent groups. There does seem to be a slightly greater incidence in the urban population as compared to the rural group.

Specific etiologic factors must, of course, be highly regarded. The inhalants, as in other allergies, play a very major role. The various pollens (tree, grass, and ragweed), house dust, fungi (alternaria and hormodendrum being the most frequent offenders), industrial inhalants (such as flour, tragacanth, gum arabic, and karaya gum), leather and hides in the tanning industry, furs and paraphenyleneamine dyes—all play important parts in the cause of asthma. Among the ingestant factors, such important foodstuffs as wheat, milk, eggs, corn, fish, nuts, and citrus fruits seem to play a major role. Injectants, too, are frequently responsible for the disease. Such important biologicals as insulin and liver extracts are to be thought of in patients receiving such therapy. In addition, thiamine chloride, the arsenicals, the various sera, and many others are capable of producing trouble. Drugs also play an important part. Aspirin is known to be a frequent offender, more often than is generally believed by physicians. Also sulfonamides, various chemical dyes, quinine, bromides, barbiturates, and a host of other drugs have been incriminated. Bacterial causes of asthma have long been known, but not easily proven. The common respiratory organisms have often been removed and cultured from bronchoscopic aspirations as well as from sputa collected in sterile containers, yet adequate and specific skin testing has not been forthcoming. Swineford studied nucleoprotein and carbohydrate fractions of various respiratory organisms (14 different bacteria), performing 3860 tests with various fractions, and yet was unable to come to any definite conclusion, other than that further study was required. As in other phases of medicine, psychogenic factors may play a very important part. Certainly, more is appearing in the literature on this subject with each passing year. The allergist as well as the internist is more aware of this possibility in mind, in dealing with chronic recurrent asthma. Last, but by no means least, are certain miscellaneous factors, including the endocrines, viz., thyroid, ovarian, pituitary, and adrenals, and also the physical causes of allergy, such as light, cold, and heat.

Pathogenesis

It is generally assumed by most allergists, as well as others who see bronchial asthmatics frequently, that the pathogenesis of this disease is as follows: that an immunologic reaction occurs when a specific allergen comes in contact with sensitized cells in the living mucosa of the bronchi, and that histamine is released in quantity sufficient to create an alteration in the normal physiology in that tissue and organ. This reaction would tend, in part at least, to explain a fact upon which all agree: that the asthmatic paroxysm is accompanied by marked narrowing or constriction of the bronchial lumen. The histamine theory, as a basis for all allergies, is the one most commonly accepted today. Histamine itself is a chemical entity of small molecular weight, 111. Because of its size, it diffuses very rapidly throughout the body, and is responsible for the whealing reaction. However, as Abramson so well points out, the histamine theory does not answer all the questions in all allergies. The following are several factors which are not compatible with the histamine theory:

1. Much of the data in the literature consists of biological assay, in which claim is made without proof that histamine is the active agent.

2. Wheals produced by light, cold, and stroking do not show pseudopods, and if a small molecule like histamine were responsible, pseudopods would be formed in some cases.

3. Schiller and Lowell showed that anti-histamine drugs can control bronchial spasm produced by histamine, but not by true allergens, yet both are controlled by epinephrine.

4. There is no release of histamine or an equivalent "H" substance when a sensitized uterus contracts in a suitable medium.

5. The Arthus phenomenon cannot be reproduced even by sizeable doses of histamine.

The above are only a few of the many valid arguments now known which tend to upset the histamine theory as the major basis for true allergic reaction. Only time and continued research will yield the true answer.

The physiologic mechanism involved in an attack of bronchial asthma may be briefly outlined as follows:

The allergen-reagin reactions causes bronchiolar constriction, edema of the mucosa of the bronchial tree, and increased secretion of mucus. These three factors combine to produce bronchiolar obstruction, which seems responsible for the signs and symptoms in the early stages of an attack. From this, there develops decreased alveolar ventilation which causes: (a) increased CO_2 tension in the alveoli and in systemic arterial blood, which in turn causes stimulation of the respiratory center, and also sets up renal mechanisms to compensate for respiratory acidosis; and (b) decreased oxygen tension in alveoli and in systemic arterial blood, which is responsible for reflex respiratory stimulation via the carotid body and aortic body reflexes, cyanosis, and increased hemoglobin and erythrocyte count.

Pathology

There is a lack of unanimity of opinion as to the true pathologic picture caused by bronchial asthma. Actually, death from primary bronchial asthma is a rarity, except in severe status asthmaticus, yet numerous autopsy reports have appeared in the literature of patients who have had asthma for variable periods of time and died of some intercurrent condition. The fundamental pathologic features were well described by Huber and Koessler in 1922. There are no strictly distinct findings at post mortem. All conditions present may be found in other disease also, but certain changes occur so regularly, that they may be called "characteristic." Essentially these consist of:

1. Emphysema with distention of the alveoli.

2. Increased thickness of the bronchial wall with narrowing of the lumen.

3. Increased thickness and infolding of the mucosa.

4. Excess mucus in the lumen with plugs of thick tenacious mucus and fibrin.

5. Dilatation of the small bronchioles and alveoli.

6. Cellular infiltration of the mucosa, submucosa, mucous glands, and at times, the musculature with eosinophiles, plasma cells, and lymphocytes.

7. Thickening and hyaline degeneration of the basement membrane.

8. Hypertrophy of the bronchial musculature.

9. Degeneration of the mucous glands.

Most investigators agree that the important findings are: thickened basement membrane, eosinophilic infiltration, varying hypertrophy of the bronchial musculature, widened submucosa, degeneration of the mucous glands, and varying degree of right ventricular hypertrophy.

The latter finding has created considerable controversy, since not all authors agree on any characteristic pathology in the heart in bronchial asthma. Criep has shown by studies on experimental anaphylaxis in the guinea pig that various arrhythmias and auricular or ventricular asystole followed by cardiac arrest may occur. However, this phenomenon may also be found in asphyxia. Alexander reported that of 15 autopsies on asthma sufferers, 5 were associated with superimposed disease, and of the remaining 10, two showed right ventricular hypertrophy, two had right ventricular dilatation, and the remaining six revealed no pathologic cardiac changes. Alexander also noted that in vivo, during an asthmatic attack, the heart often appears radiologically smaller than normal. He believed that with bronchospasm there may be diminished cardiac filling due to decreased intrathoracic negative pressure. The major evidence, however, suggests that in the absence of complicating disease, including emphysema, the heart is

not seriously damaged even in long-standing bronchial asthma.

Symptoms

Rackemann divides asthma into six groups:

I. *Asthmatic bronchitis,* as with "colds." These patients may also be allergic to extrinsic factors.

II. *Vasomotor rhinitis* with negative skin tests, often in young adults and often followed by severe asthma.

III. *Bacterial allergy,* especially in the older age group of asthmatics, in which environment and foods are not factors.

IV. *Depletion,* as when asthma is complicated by somatic factors, e.f., weight loss, exhaustion, and psychic trauma.

V. *Polypoid sinusitis* with asthma, in which the nasal lesions are part of the picture and not the cause of the disease.

VI. *Emphysema* is part of every attack of asthma, reversible in the acute, and irreversible in the chronic stage.

For better understanding, the symptoms of bronchial asthma must be divided into the three major types encountered in medical practice, viz: acute, chronic, and status asthmaticus.

Acute attack

1. Sudden onset.

2. Dyspnea early, with orthopnea later.

3. Wheezing, especially nocturnal.

4. Slight cough early, with increased cough and expectoration later.

5. Relieved by epinephrine, at least for short interval.

Chronic Bronchial Asthma

This form is usually preceded by repeated attacks, or it may follow a single acute attack.

1. Attacks of dyspnea are frequent, almost daily, usually worse on exertion and at night.

2. Cough with expectoration, wheezing, emphysema, usually not relieved by epinephrine, except early.

3. Diminished vital capacity—the greater the asthma, the lower the vital capacity.

Status Asthmaticus

1. Onset as with the acute or chronic form, or it may be a progressive continuation of either of the above.

2. Severe orthopnea.

3. Cyanosis.

4. Exhaustion.

5. Vomiting frequently.

6. Dehydration.

7. Weight loss.

8. Hypochloremia.

9. Hemoconcentration with elevated hematocrit.

10. By bronchoscopy:

    (a) hemorrhagic redundant mucosa, decreased tracheal lumen as well as bronchial lumen.

    (b) thick, tenacious secretions with plugs.

    (c) on expiration, collapse of the posterior tracheal wall.

    (d) increased negative pressure, which causes an increase in pulmonary capillary blood pressure, with transudation into the alveolar spaces. Blood flow is increased in the chest, with more in the left ventricle, progressive accumulation of blood in the lungs and increased capillary blood pressure with congestion, transudation, and finally pulmonary edema.

Associated Symptomatology. Chronic emphysema as well as subcutaneous or mediastinal emphysema may also occur. These may be treated, with the asthma, by prolonged bed rest, although needling may have to be done to relieve the air pressure in the mediastinal form. Cutting down above the sternal notch may occasionally be required in order to release the air.

Diagnosis

Direct diagnosis. This is established on the basis of:

    (a) History, including family history.

    (b) Onset.

    (c) Physical examination.

    (d) Chest X-ray.

    (e) Nasal and sputum smears for eosinophiles, Curschmann's spirals, and Charcot-Leyden crystals.

    (f) Therapeutic response to epinephrine.

    (g) Skin testing.

Differential diagnosis

1. Asthmatic bronchitis

Associated with coryza, fever, poor response to sympathomimetic drugs, preponderance of neutrophiles in the secretions, and increased sedimentation rate.

2. Foreign bodies in bronchus.
   (a) History.
   (b) X-ray.
   (c) Bronchoscopy.

3. Ayerza's Disease

Rare, dyspnea, polycythemia, chronic cyanosis, a prominent pulmonary conus with hypertrophy of the right ventricle and right axis shift.

4. Pertussis
   (a) Not relieved by epinephrine.
   (b) Lymphocytosis.
   (c) Culture plate for hemophilus pertussis.
   (d) Absence of eosinophilia.
   (e) Typical whoop.

5. Bronchotetany
   (a) Mostly in children.
   (b) Rare condition.
   (c) Dyspnea with wheezing.
   (d) Relieved by calcium intravenously.

6. Cardiac asthma
   (a) Nocturnal paroxysmal dyspnea.
   (b) Left ventricular strain or failure.
   (c) Hypertension with aortic defect.
   (d) Prolonged circulation time.
   (e) Associated diminuation in minute volume.
   (f) Accumulation of metabolic products by anoxemia and embarrassment of respiratory center.
   (g) Response to digitalis.

7. Bronchogenic carcinoma
   (a) Mostly males between the ages 50 and 60 years.
   (b) Usually the central one-third of the lungs, near the hilum, is involved.
   (c) This is the third most common primary malignancy found in the human.
   (d) Early in this condition, there is cough, with or without hemoptysis, followed by atalectasis, pneumonitis, or abscess.

8. Pulmonary tuberculosis with an asthmatoid picture.
   (a) History of contacts.
   (b) Physical examination.
   (c) X-ray of chest.
   (d) Positive sputum.
   (e) The two conditions may co-exist (this is rare).

9. Industrial dusts
   (a) Asbestosis with fibrosis.
   (b) Talc placques, in talc workers.
   (c) Bauxite inhalation leads to fibrosis due to the inhalation of aluminum particles.

10. Cor pulmonale
    (a) Hypertrophy of the right ventricle with pulmonary fibrosis.
    (b) Rare in pure bronchial asthma.
    (c) Increased heart size to the right.
    (d) Prominent epigastric pulsation.
    (c) Accentuation of pulmonic second sound.
    (f) Right axis shift.

11. Fungus infection of the lung
    (a) Examination of sputa for actinomycosis, blastomycosis, coccidioidomycosis, torulosis, moniliasis, histoplasmosis.
    (b) Histoplasmosis with pulmonary calcifications on x-ray, especially in East-Central U.S.A., yielding positive reaction with histoplasmin, and occurring more often in the Negro.

12. Filariasis due to *Wuchereria bancrofti*.
    Skin test with *Dirofilaria immitis* antigen-positive in 1:8000 and 1:16,000 titres.

13. Tropical eosinophilia
    (e) Chiefly in tropics.
    (b) Insidious onset with malaise, low grade fever, headache, non-productive cough, wheezing, dyspnea, leucocytosis up to 60,000, blood eosinophilia up to 89%. X-ray reveals fine mottling in both lungs.
    (c) Responds rapidly to intravenous neoarsphenamine.

14. Loeffler's syndrome
    (a) X-ray shows patchy infiltrations with clearing and recurrence.
    (b) Fever, cough, dyspnea, wheezing, leucocytosis, eosinsphilia up to 84%.
    (c) Responds to adreno-corticotrophic hormone injections, with disappearance of eosinophiles in 6 to 8 hours, and decrease in transitory pulmonary infiltrations, as shown by X-ray.

15. Periarteritis nodosa
   (a) History of allergy in 33%.
   (b) Exact etiology is unknown.
   (c) Believed due to an allergy.
   (d) Hyperergic response, especially in the capillaries and peri-arterial tissues.
   (e) This is a collagen disease, similar to disseminated lupus erythemaosus, dermato-myositis, and rheumatic disease with Aschoff bodies.

Prognosis

1. Life insurance actuarial figures reveal an increase in the death rate in asthmatics, higher for women than for men.

2. Such figures are obtained not from 100% autopsy reports, but simply from death certificates showing "asthma" as the "cause of death"—facts drawn only from clinical interpretations.

3. From actual experiences of allergists, it is felt that the span of life in the ordinary asthmatic is not altered.
   (a) Life span in the continuous form is distinctly shorter than in the spasmodic or intermittent type.
   (b) Most deaths from asthma occur in the status asthmaticus type.

Treatment

The basis of therapy in asthma is, as in other allergic diseases, avoidance and/or hyposensitization. Poor results are usually due to:

1. Stopping treatment too soon.
2. Interrupted dosage schedule.
3. Continued contact with offenders.
4. Incomplete testing, with failure to discover all responsible factors.
5. Active foci of infection in the respiratory tract.
6. Situational factors, emotional and psychic.

Active therapy must be divided into three parts:
1. Acute attack.
2. Chronic bronchial asthma.
3. Status asthmaticus.

The acute attack. 1. Epinephrine hydrochloride 1:1000 aqueous solution, minims 3 to 6, subcutaneously, repeated as often as needed.

2. Aminophyllin, grains 3¾ to 7½, intravenously, slowly and with caution.

3. Suppositories aminophyllin, grains 7½.

4. Orally, ephedrine, grains ⅜ to ¾ (the British use grains 3 to 5), with or without a sedative, such as phenobarbital or other barbiturates.

5. Combined tracts (several available on the market) containing ephedrine, theophylline, and phenobarbital.

6. Other sympathomimetic drugs, such as sublingual isuprel or aleudrin, oral sprays of epinephrine 1:1000, various other aqueous bronchial antispasmodics, dry powder inhalations of nor-isodrine (Abbott). The latter must be used with caution, in order to minimize side effects of the drug.

Chronic asthma: 1. Epinephrine hydrochloride 1:1000 aqueous, minims 3 to 6, subcutaneously; epinephrine in oil 0.5 to 1.0 cc., intramuscularly; epinephrine in gelatine, 1:500, 0:5 to 1.0 cc., intramuscularly.

2. Aminophyllin, intravenously (best), or per rectum as suppository or retention enema; orally this drug is relatively ineffective.

3. Ephedrine, orally, ⅜ to ¾ grains, usually with a sedative. The British recommend ephedrine in 3 to 5 grain doses, orally, several times daily.

4. Combinations of ephedrine with aminophyllin (theophylline) and phenobarbital. Several good ones available in tablet, plain and enteric coated, and also capsules, viz. tedral, amesec, luasmin, franol, etc.

5. Orthoxine, a new sympathomimetic drug, like ephedrine except for fewer side reactions, an active bronchodilator with little pressor or central nervous system side effects.

6. Oral inhalations with 1:100 epinephrine in a nebulizer, 1:200 vaponephrine, aleudrin solution, butanefrine 2% solution, and numerous others available on the market.

7. Anti-biotics, where chronic infection plays a major role. Penicillin, preferably intramuscularly; streptomycin, in similar manner; sulfonamides, orally; any of these by aerosol inhalation are also effective.

8. Vaccines, autogenous or stock, in

graduated doses, at regular intervals over a long span of time.

9. Bronchoscopy, with removal of mucus and plugs, followed by instillation of iodized oil, both for study and for treatment.

10. Digitalis, only when indicated.

11. Gay's mixture (so-called), which, because of the arsenic in its formula, requires close watch over the patient.

12. Psychotherapy, where required.

13. Miscellaneous, such as x-ray, surgical treatment of sinuses or bronchiectasis.

14. Specific therapy, including avoidance of foods or inhalants, and specific hyposensitization against pollens, molds, and dusts.

Status asthmaticus. 1. Oxygen, 100%, by B.L.B. or pressure mask; or oxygen-helium mixtures, in 20% and 80%, respectively, or other combinations, such as 30 and 70%, and even 40 and 60% mixtures. This should be a hospital procedure.

2. Aminophyllin, intravenously, by continuous drip, 2 to 3 grams in 2000 cc fluids.

3. *Never* use morphine, despite occasional suggestions to the contrary, as offered by rare authors. Demerol 50 mg., repeated as needed, seems to be safe; barbiturates, orally, rectally, and intramuscularly are of help.

4. Ethyl alcohol, 5%, intravenously in 5% glucose-saline, with or without 0.3 cc. to 1.0 cc. epinephrine, at 100 to 120 drops per minute.

5. Maintain blood chlorides at normal level with intravenous saline.

6. Bronchoscopy may often be a life-saving measure.

7. Other methods which may help are: ether anesthesia, ether in oil, as retention enema, or intramuscularly; novocaine in 0.1% solution, intravenously;

coramine, 5 cc. intravenously and repeated, has been given with good results in some severe cases; the antihistaminics, alone, seem of little value, other than to reduce mucus secretion slightly, but when combined with aminophyllin or with aminophyllin and ephedrine seem to help some.

Because of lack of space, I did not enter into minute details on many phases of the subject. Suffice it to say that I have covered the most important points on the subject of bronchial asthma, have mentioned some of the controversial aspects, and leave the reader to acquaint himself with newer concepts concerning the immuno-chemistry and therapy of this disease as it becomes available in the literature.

BIBLIOGRAPHY

1. Abramson, H. A.: The present status of Allergy. The Nervous Child, Vol. 7, No. 1, Jan. 1948.
2. Alexander, H. L.: Synopsis of Allergy; J.A. M.A., 136, Feb. 28, 1948.
3. Curry, J. J. and Lowell, F. C.: J. Allergy, 19:9, 1948
4. Feinberg, S. J.: Allergy in Practice.
5. Glaser, J.: Pediatric Allergy. A critical review of recent literature, Ann. Allergy, 6:178, 1948.
6. Herxheimer, H.: Aleudrin and anthisan in bronchial spasm. Lancet, London 1:926, 1948.
7. Simon, S. W.: Nethaphyl in Bronchial Asthma, Ann. Allergy, 6:662, 1948.
8. Spatt, S. D. and Grayzel, D. M.: Cor pulmonale. Am. J. Med. 5:252, 1948.
9. Sterling, A., et al: Massive doses of penicillin in chronic asthmatics. Am. Pract. 2:570, 1948.
10. Unger, L., and Gordon, B. F.: Ann. allergy, 7:397 and 7:551, 1949.
11. Vaughan-Black: Practice of Allergy, Second edition.
12. Wittich, F. W.: A clinical evaluation of Orthoxine in the treatment of allergic diseases. Ann. Allergy 6:664, 1948.

ACUTE PULMONARY EDEMA*

ALDO A. LUISADA, M.D.**

The topic I am going to discuss today still is controversial. Don't expect the last word on this subject as there is much to learn as yet about the chronic and the paroxysmal types of pulmonary edema. These forms shall be kept separate because they are different in regard to both the mechanism of production and the treatment to use.

Clinically, paroxysmal pulmonary edema is an acute attack of dyspnea, accompanied by oppression in the chest, sometimes reaching the stage of pain, and followed by abundant expectoration of foamy fluid, frequently tinged yellow or pink.

On physical examination, one finds widespread rales on the chest, from the small crepitant alveolar rales to the tracheal gurgles. These rales are supposed to start at the bases but actually sometimes start suddenly all over the chest. They are of different caliber because they are caused by fluid in all of the air passages.

It is characteristic of the attack to start suddenly, more often during the night but occasionally also during the day.

Anatomically, edema means infiltration of serum in a tissue. Actually, as the lung tissue is so thin, as soon as the infiltration starts, the fluid passes into the alveoli. Therefore, one should speak not of edema but of transudation.

One should keep in mind the fact that acute pulmonary edema is a condition which can be associated with multiple etiology and that many diseases may cause it, some connected with the heart, others entirely unrelated. Usually pulmonary edema is discussed with heart disease. It is sometimes described in the chapters dealing with chest, traumatic or nervous diseases. This is only because the authors do not consider the

syndrome in its entirety. However, it is possible that the type of pulmonary edema which occurs in one condition is not so different from the others in its mechanism of production.

I have been working for over twenty years on problems related to pulmonary edema. This was considered once as a common event in uremia, but since then, there have been changes in the percentage of conditions associated with the syndrome.

The diseases which can present acute pulmonary edema are the following:

Heart Diseases

(1) The edema occurs most frequently in a group of patients presenting strain of the left ventricle caused by aortic insufficiency, either luetic or rheumatic, or by hypertension.

(2) It occurs often in coronary heart disease, and especially in patients with recent acute coronary occlusion.

(3) Condition of strain of the right ventricle. Once in a while there is an isolated report of acute pulmonary edema in cases with chronic cor pulmonale. There also have been a few reports of acute pulmonary embolism followed by diffuse pulmonary edema.

(4) Mitral insufficiency and stenosis. It is common to observe pulmonary edema in this condition. It is even more common in pregnant women, either during the last two or three months of pregnancy or during labor. In these cases the left ventricle is not submitted to particular strain while the right ventricle suffers most.

Acute pulmonary edema occurs often if a patient *inhales toxic gases*. This occurred often during the first World War and is not unusual even now in industrial plants. When phosgene was inhaled, pulmonary edema was confused with bronchopneumonia.

In cases of *drowning*, fresh water or salt water may penetrate the air passages and kill the patient by causing acute pulmonary edema. Actually, in many of

these cases, autopsy shows that the lungs are full of edema fluid and not of water.

In certain cases, *foreign bodies distend hollow viscera*, like a bronchus or the esophagus, or there is distention of the stomach or gall bladder. Acute pulmonary edema may occur either during distention or at the time of emptying of the hollow organ by the physician. I wish to mention a particular case. A woman of fifty-eight was eating meatballs which she could not chew properly. One of these was caught in the esophagus, and the patient presented a picture of suffocation, and expectorated large amounts of foamy fluid. Brought to the hospital, she was considered in agony. After twenty-four hours, however, the patient was still alive and the meatball was removed; then the edema of the lung subsided, and the patient recovered. No cardiovascular disease was found to be present.

Acute distention of the stomach was considered frequent a century ago. When a patient had a distended stomach after ingestion of three or four quarts of food and fluid, as was then frequent, and an acute attack followed, death was thought to be caused by indigestion. Some of these were cases of coronary occlusion, and the filling of the stomach was incidental; others were cases of acute pulmonary edema.

Pulmonary edema is not infrequent in lesions of the central nervous system and, occasionally, of the peripheral nervous system. The following conditions shall be considered:

(1) *Skull fracture.* If the fracture does not cause immediate death and permits survival of from 12 to 24 hours, the patient may die later of pulmonary edema.

(2) *Subarachnoid hemorrhage.* I shall mention a case of my observation. A woman of forty had an acute fainting attack which was followed by severe pulmonary edema. Morphine was employed and, after a few hours, her condition became good. Then the clinical signs of subarachnoid hemorrhage became apparent. The patient recovered and no cardiovascular or renal disease was discovered. The hemorrhage caused the fainting attack and had a strict relationship

with the acute attack of pulmonary edema.

(3) *Encephalitis, meningitis, polio, cerebral embolism, cerebral thrombosis* or *hemorrhage* are not infrequently followed by pulmonary edema. In one of my patients, a cerebral embolism started from a pulmonary abscess and was followed by pulmonary edema. Bronchopneumonia occurred later and the patient died after several days. The edema of the lung was unilateral, a fact which is rare; the embolization was found on the same side as the pulmonary edema, both in the olive and in the thalamus. Dr. Farber has studied several cases of pulmonary edema in children, connected with diseases of the central nervous system.

The importance of the sympathetic nervous system is revealed by experiments on the stellate ganglion and by the fact that, in the first reports of Danielopolu on surgery for angina pectoris, the manipulation of the ganglia caused acute pulmonary edema and death in several cases.

Scattered studies on *allergic diseases* report acute pulmonary edema, at times during allergic shock. The edema of the lungs is often associated with edema of the glottis. The latter may start first and favor the occurrence of the lung edema.

There are cases of *thyroid* or *beriberi heart* which present attacks of pulmonary edema.

Other conditions are of main interest to the surgeon:

(1) *Injury to the chest.* Localized injury to the chest may be followed by edema of both lungs. "Wet lung" is a bad term for pulmonary edema.

(2) *Conditions of medical or surgical shock.* The edema is at times less acute and the onset is less obvious because obscured by the symptoms of shock. We should remember that, in many of these cases, there is a condition of "overloading of the cardiovascular system" caused by repeated, excessive transfusions. This is proven by the fact that such cases were rare thirty years ago, so that the cases with acute pulmonary edema were found only in the medical wards. The rapidity and the amount of transfusion has a direct effect on the occurrence and sever-

ity of the edema, and frequently, the more fluid the patient gets, the more severe becomes the pulmonary edema. The normal vascular system can stand transfusion in large amounts whenever the nervous system and the heart are in good condition. On the other hand, if these are weakened or defective, small amounts of fluid can start the edema. I remember studies made in 1939 with slow infusion of heparin in patients with sub-acute bacterial endocarditis. Even when the fluid was given by the drip method, the slight increase of circulating fluid was sufficient to overload the heart and frequently initiated pulmonary edema.

I am now coming to the most controversial point, namely, the *pathogenesis of acute pulmonary edema*. Apart from clinical observations, there have been several methods of producing pulmonary edema in animals. Acute pulmonary edema may be induced by intravenous adrenalin in rabbits; by ammonium salts in rabbits, rats, or guinea pigs; by phosgene gas in several species; by the rapid intracarotid infusion of salt solution in dogs or rabbits. Normal dogs can stand enormous intravenous infusions of fluid and even three times the blood volume of physiological salt solution can be introduced without damage. On the other hand, I was able to show with my co-worker Dr. Sarnoff, that rapid infusion into the common carotid arteries toward the brain constantly causes pulmonary edema.

The studies on the mechanism of acute pulmonary edema have been numerous.

I shall mention only a few among the various conclusions reached through animal experimentation:

Extreme increase of pressure in the left auricle does not cause pulmonary edema. Most types of paroxysmal pulmonary edema can be inhibited by narcotics and anesthetics, chloral hydrate and morphine being the best. Sympathectomy and sympatholytic drugs prevent or reduce the severity of pulmonary edema, as has been shown in pulmonary edema caused by rapid intracarotid injection of fluid; by ammonium salts; by adrenalin; or by trauma to the chest.

It had been noted long ago that dam-age to the left ventricle may cause acute pulmonary edema. Later, it was shown that damage to the right ventricle may lead to the same result though with less frequency.

In several types of acute pulmonary edema in animals, the first droplets of fluid from the trachea have a chemical constitution which is extremely poor in proteins, being more like a transudate than an exudate. Then the fluid becomes richer in proteins, and sometimes blood tinged. This observation of the Koenigs may be explained by admitting that there is an acute condition, still partly unknown, which causes transudation of fluid; the latter leads to blocking of some of the air passages and to anoxia of the lung; the result of anoxia is exudation of fluid.

Acute pulmonary edema is favored by high pressure and increase in permeability in the pulmonary capillaries. The two elements are not necessarily connected and may be supplemented by a third, namely, damage to the capillary wall.

High pressure in the lesser circulation favors pulmonary edema. This is obtained whenever abundant venous return and high resistance are present. A similar situation occurs in a patient with chronic hypertension in which venous return to the heart is increased by exertion, excitement, or an abundant meal.

The increased permeability of the pulmonary capillaries may be caused by changes of the chemical content of the blood. However, patients with peripheral edema present acute pulmonary edema only occasionally. The typical cases have a dry skin, no ascites, and, in contrast, a "wet lung." Chemical changes may have only a collateral importance if they produce results only in the lungs.

Among the several factors which have been studied we should quote the possibility that nerve impulses may increase the permeability. These may act in several ways:

(1) By blocking or narrowing the pulmonary venules.

(2) By dilating the pulmonary arterioles or capillaries.

(3) By increasing the capillary permeability, independently of any caliber change.

Experimental studies seemed to prove that sympathetic stimulation may increase the permeability of the synovial serosa of the knee in contrast with vasoconstriction. Later, Sarnoff studied the permeability of the capillaries of the legs and showed that sympathetic stimulation decreases the blood flow but increases the amount of lymph flow. The same experimental study shall have to be repeated for the lungs before it can be applied to the interpretation of pulmonary edema.

As I told you already, previous sympathectomy decreases the mortality of the animals and the severity of the edema of the lungs, and the same result is obtained by drugs inhibiting the sympathetic system.

I would like now to clarify a term which has been employed often, that of "neurogenic pulmonary edema" as opposed to the older conception of pulmonary edema due to "left ventricular failure." The term *neurogenic* should be interpreted as meaning that, in the mechanism of the attack, nerve impulses are of paramount importance. These impulses may cause vasoconstriction or dilatation, therefore varying the work of the heart; may cause tachycardia or bradycardia; may vary the venous return, therefore overloading or depleting the lungs; may possibly cause changes in the caliber of the pulmonary vessels; last, they might increase the permeability of the pulmonary capillaries. All these phenomena can be modified and supplemented by hormones and by chemicals, both of which are often mobilized by the central nervous system. One should not forget, further, the great importance that *anoxia* has for the lung capillaries and the damaging effect that *dyspnea* may cause, especially if there is spasm of the glottis, so that severe suction favors outpouring of fluid from the capillaries.

The possibility that chemicals or local hormones may increase permeability is now being investigated in certain laboratories. It is possible that, in heart failure, substances can be found in the blood which damage the capillary wall.

I can remember that, twenty years ago, my co-workers and I were playing with the idea that histamine or acetylcholine, produced in the lung, led to edema of this organ. We could not obtain certain proof of this fact. If it could be proven that sympathetic stimulation leads to liberation of acetylcholine within the lung, then the local effect of this substance might favor transudation of fluid.

The role of anoxia deserves further discussion. We know that the pulmonary capillaries get oxygen directly from the alveoli. If the bronchioles are blocked, no oxygen can be absorbed. Therefore, once the attack has started, anoxia may play an important role in damaging the capillary wall and increasing the exudation of fluid.

In the older times the accepted theory was that of an acute insufficiency of the left ventricle. I have to remind you now that some people do not believe in the existence of the acute insufficiency of one ventricle, at least in the older meaning. If there is an acute failure of the left ventricle, the right cannot maintain its output for long because the venous return becomes inadequate; the septum weakens its contraction; and the coronary flow to the right ventricle may also become insufficient.

One may admit that pulmonary edema can be caused by different mechanisms or one may try to explain all the various types of this syndrome by admitting a common mechanism. In the last case, the conception of the left ventricular failure has to be abandoned.

In certain cases, especially in cardiac patients, there is strain and dilatation of the left ventricle. However, strain should not be confused with failure and it shall be noted that it may be the cause of nerve stimuli leading to vascular and visceral reflexes. Between left ventricular strain and paroxysmal pulmonary edema, there is a long chain of events and some of the links may vary in the different types.

I am now going to attempt to sketch the possible sequence of events in one type of acute pulmonary edema, that caused by trauma to the skull (Fig. 1).
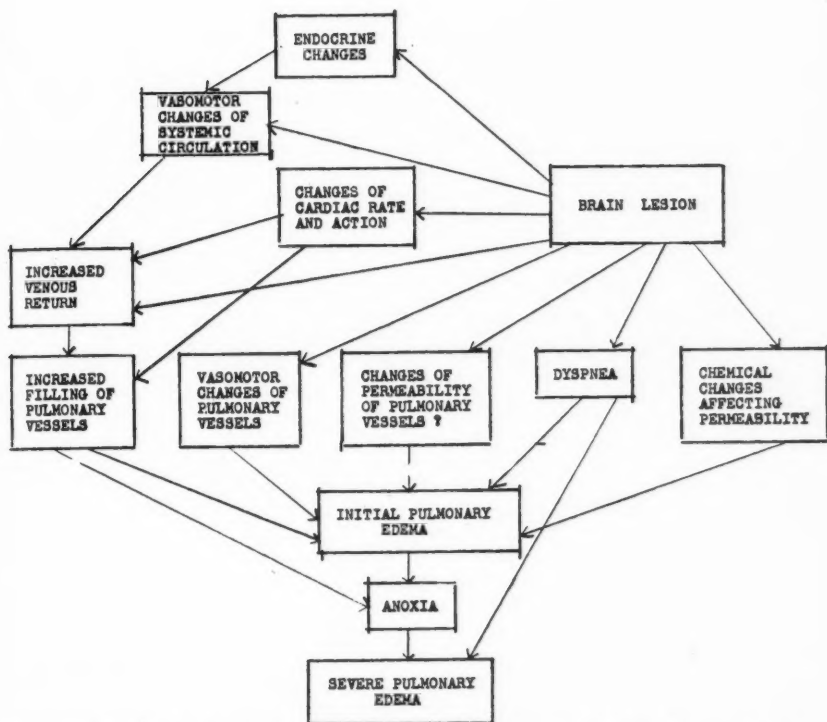
SKETCH OF MECHANISM OF ATTACK IN ACUTE PULMONARY EDEMA FOLLOWING A BRAIN INJURY OR HEMORRHAGE

Figure 1

This type could be called *direct pulmonary edema*, while others might be called forms of *reflex pulmonary edema*. In the latter, a different sketch should be drawn (Fig. 2).

If the patient has failure of the left ventricle, there may be a mechanical factor added to the others, but it should be kept in mind that failure alone is unable to produce the acute pulmonary edema.

What I say now is a simple speculation and has not been proven as yet. It should be added that probably other links of the chain exist, like the local production of "edematogenic" substances following nerve impulses, or the chemical changes of the blood taking place in certain heart conditions.

We shall now discuss the most important problem, that of *treatment*. In most of these cases, treatment with anesthe-

tics and narcotics is useful, either as a preventive or during the attack. Morphine is definitely good.* I was the first, twenty years ago, to advocate the intravenous injection of morphine. Two years ago an Argentine rediscovered the same technique. The I.V. injection of morphine in doses of 10 to 15 mg. (⅙ to ¼ grain) should be done slowly, and possibly repeated after one-half hour if not effective. In general, no atropine should be added unless there are special indications for it or the patient has a coronary occlusion with a slow pulse. The proof that atropine may favor pulmonary edema has been given by experiments with intracarotid infusion of sa-

---

* A reserve should be made for cases of pulmonary edema secondary to cerebral injuries and for cases in shock where morphine may be detrimental.

line solution. Actually, atropine was added to morphine over 100 years ago in England when physicians did not know the difference between cardiac asthma, bronchial asthma, and acute pulmonary edema.

Other central depressants have a favorable action. Phenobarbital and other barbiturates are usually good though chloral hydrate has been found the best. Long ago, I advocated the intravenous injection of 0.3 gm. of chloral hydrate in addition to morphine, in 20 cc. of solution. However, one should not give chloral hydrate if the patient is in shock or in cases with injury or disease of the central nervous system.

Chloral hydrate is also good as a prophylactic. Hypertensive patients may receive chloral hydrate by mouth every night in doses of 1 gm.

Dibenamine is a new drug and has been applied to clinical cases only recently. It should prove useful in several cases, especially if there is hypertension. As it causes a drop in blood pressure, I would not give it in shock or whenever there is low blood pressure.

Hypotensive drugs and vasodilators may be useful as prophylactics and, among them, aminophyllin is one of the best. Mercurial diuretics have been proven useful during the attack; they lower the pressure in the pulmonary artery.

Digitalis may be used as a prophylactic in patients with dilatation of the left ventricle and left ventricular strain. It has definitely decreased the frequency of attacks of pulmonary edema in cases of hypertension.

Oxygen is useful during the attack, and especially so if given under pressure, as it has been shown by Barach. It should be given in 50 per cent concentration, and
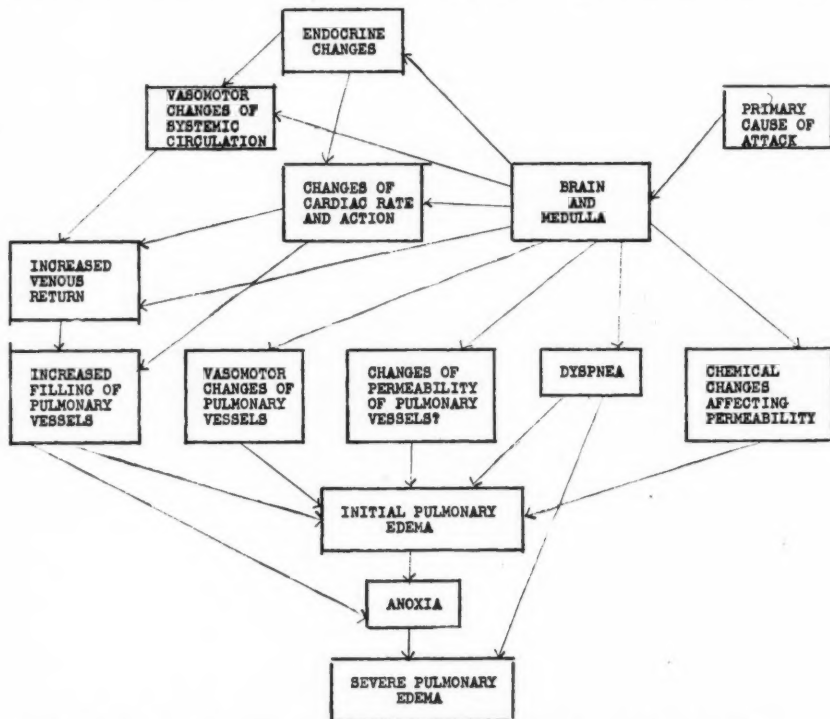
SKETCH OF MECHANISM OF ATTACK IN ACUTE PULMONARY EDEMA NOT RELATED TO BRAIN LESION.

Figure 2

the pressure should not be too high, in order not to injure the mucosa of the bronchi. Expiratory masks may be used, which oblige the patients to exert themselves and to raise the expiratory pressure to between 4 and 6 cc. of water. However, I suppose that in many of the surgical patients this expiratory strain would be contraindicated.

Recent experiments in my laboratory with anti-foaming agents have shown that *alcohol* vapors inhaled during the attack, have an extremely favorable action by decreasing the foam and preventing anoxia and suffocation. If confirmed by clinical experience, treatment with alcohol vapors will be added to other measures (drugs, oxygen under pressure, etc.) and should be used in all cases of acute pulmonary edema, irrespective of the cause.

It should be kept in mind that removal of noxious stimuli should be attempted whenever possible. For the surgical patient, I wish to emphasize the need of *not giving too much fluid by vein* in order not to overload the vascular system. Even if they have a normal heart, surgical cases experience a trauma which may lead to increased sensitivity of the heart and greater reactivity of the pulmonary vessels. Whenever shock is impending or existing in surgical or coronary patients, one should give concentrated plasma by adding only one-half volume of water to dry plasma and always avoid plain saline solution.

I wish to remind you also of the older system of treating paroxysmal edema, namely by venesection. This is useful during the acute attack by interrupting a vicious circle and may favor the action of drugs. It should not be employed in patients in shock, or with low arterial and venous pressure.

Discussion

Dr. Zimmerman: From the surgical point of view the lecture has opened up new vistas. Are there any questions?

Dr. Langendorf: Do you advocate the prophylactic use of strophanthin, or the administration of strophanthin during the attack of pulmonary edema?

Do you think that mercurial diuretics may be useful in the prophylaxis of pulmonary edema?

Dr. Luisada: Personally, I would not advocate the use of digitalis or strophanthin during the attack and I am extremely doubtful about the theoretical background which led to their use. Even if we believe that the left ventricle is weak and the right is strong, how do we know that digitalis increases the work of the left ventricle and not that of the right? Still, I must admit that facts are more important than speculations. If you have tried strophanthin and have been favorably impressed, this counts more than all other considerations. In general, I believe that it is better to decrease rapidly the load on the heart during the attack and to start digitalis when the signs of the pulmonary edema have subsided. Mercurial diuretics can be used as prophylactics, especially if there is accumulation of fluids in the interstitial tissues (latent edema); in such cases they might be helpful. Their acute action in decreasing the pressure of the pulmonary artery has been demonstrated recently and may suggest their use during an attack.

Dr. Ravenna: How would you differentiate acute pulmonary edema from bronchopneumonia?

What do you think of inflammatory edema and especially of that which may accompany rheumatic fever?

What about edema caused by phosgene?

Dr. Luisada: If there is fever and the patient has no other cause for it, this favors the diagnosis of pneumonia. Another differential datum is expectoration. If the patient is emitting abundant foam, that is more typical of pulmonary edema. In general, in pulmonary edema, you can hear rales of different caliber and extended to both lungs; in bronchopneumonia you find consolidation, and rales of small caliber in one part of the lung field. Bronchopneumonia usually develops on the side on which the patient lies or on the operated side, pulmonary edema is usually bilateral. However, at times the problem is delicate, because the patient may have started with pulmonary edema and then may have developed bronchopneumonia, or vice versa. As far

as the x-rays are concerned, it should be possible to differentiate the two forms. There have been reports of pulmonary edema starting in the hilar regions and then spreading to the rest. This is different from the picture of pneumonia.

So far, I was talking about *acute* pulmonary edema. There are also the chronic and the subacute forms of pulmonary edema to be considered. If a surgical patient starts with acute pulmonary edema, he may develop bronchopneumonia later. There is no doubt that a surgeon should give penicillin or aureomycin in order to prevent complications and should try not to limit the expansion of the diaphragm. Other possible procedures are the transfusions and the drugs given. I told you already about the importance and contraindications of both.

Inflammatory edema is usually a subacute or chronic process and may be due to either development of pneumonia in a lung with acute edema or occurrance of edema in a lung with pneumonia. Inflammatory edema, in general, was not discussed today on account of not being paroxysmal.

As far as the "rheumatic pulmonary edema" is concerned, I can state the following: Rheumatic fever very seldom develops pulmonary edema at the first attack, unless you call by that name a "pneumonia with a wet lung." Patients who get a second or third attack of rheumatic fever present with greater frequency pulmonary edema, because there are valvular defects. In such cases, the differentiation between edema and pneumonia may be difficult, though the extension of rales and the amount of expectoration may help.

Phosgene inhalation causes acute or subacute pulmonary edema. The development of this, as well as that of a secondary pneumonia, is probably favored by direct lesion of the bronchial mucosa and of the alveolar endothelium.

BIBLIOGRAPHY

1. Auer, J., and Gates, F. L.—J. Exp. Med., *26*, 201, 1917.
2. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W.—J. Clin. Invest., *25*, 639, 1946.
3. Blumgart, H. L., and Weiss, S.—Ibid., *4*, 399, 1927.
4. Boggian, B.—Minerva Med. (Torino), *2*, 967, 1929.
5. Brunn, F.—Med. Klinik.—*30*, 483, 520, 1934.
6. Cameron, G. R.—Brit. Med. J.—*1*, 965, 1948.
7. Cataldi, G. M.—Policlinico (sez. med.), *44*, 170, 1937.
8. Cloetta, M., and Anderes, E.—Arch. Exp. Path., *76*, 125, 1914.
9. Coelho, E., and Rocheta, J.—Ann. Med., *34*, 91, 1933.
10. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. de F., and Richards, D. W.—J. Clin. Invest. 24, 106, 1945.
11. Daly, I. de B—Physiol. Rev., *13*, 149, 1933.
12. Farber, S.—J. Exp. Med., *66*, 397, 405, 1937.
13. .... Arch. Path., *30*, 180, 1940.
14. Frugoni, C.—L'Edema Polmonare Acuto. Rome, Pozzi, 1930.
15. Gernez, C., and Marchandise, C.—Gaz. Hop., *106*, 483, 1933.
16. Glass, A.,—Arch. Exp. Path., *136*, 88, 1928.
17. Grossman, M.—Z. klin. Med., *12*, 550, 1887.
18. Jarisch, A.—Arch. Kreislaufforsch., *7*, 260, 1940.
19. ———— Richter, H. and Thoma, H.—Klin. Wschr., *18*, 1440, 1939.
20. Kotowschtschikow, A. M.—Z. exp. Path., *13*, 400, 1913.
21. Lambert, R. K., and Gremels, H.—J. Phys., *61*, 98, 1926.
22. Lowit, M.—Beitr. path. Anat., *14*, 401, 1893.
23. Luisada, A.—Arch. Exp. Path., *132*, 296, 313, 1928.
24. .... Medicine, *19*, 475, 1940.
25. .... and Sarnoff, S. J.—Amer. Heart J., *31*, 270, 282, 393, 1946.
26. .... Proc. Soc. Exp. Biol. and Med. (in press).
27. Meurers, K. — Z. ges. exp. Med., *46*, 135, 1925.
28. Miller, J. L., and Matthews, S. A. — Arch. Int. Med., *4*, 356, 1909.
29. Moutier, F.—Presse med:, *26*, 108, 1918.
30. Rubino, A.—Folia med., *23*, 1166, 1937.
31. Sahli, H.—Arch. Exp. Path., *19*, 433, 1885.
32. Teissier, J.—C. R. XIII Congr. Int. Med., Paris, 1900.
33. Wassermann, S.—Wien. Arch. inn. Med., *24*, 213, 1933.

CLINICAL-PATHOLOGIC CONFERENCE

From the Current Files of Mount Sinai Hospital, Chicago, Ill.

Chairman: DR. H. J. ISAACS

Dr. H. Lerner:

History.

A 23 year old white female was admitted to Mount Sinai Hospital on August 11, 1948, with complaints of intermittent dry cough, extreme dyspnea, orthopnea and tachypnea of three months duration. Her complaints were aggravated when climbing stairs. There was no history of fever, chills, muscle or joint pains. At the onset of her complaints the patient was three months pregnant. This was her first pregnancy. One week prior to admission, she went to a resort where she had a severe paroxysm of coughing which lasted the entire night. This condition persisted for several days and necessitated medical management. It was felt at that time that her complaints were on an asthmatic basis. A recent B.M.R. taken at Presbyterian Hospital had been normal. There was also a history of purposeless involuntary movements of three months duration prior to admission to this hospital. Past history failed to account for the patient's present condition.

Physical examination revealed a well developed, well nourished white female with a B.P. of 110/60, a pulse of 120 to 140 and a temperature of 98.6°. There were a few crepitant rales in both bases. Cardiac examination was negative except for tachycardia and the second pulmonic sound was louder than the second aortic sound. The uterus was palpable 2 fingers above the umbilicus. There were rapid, purposeless, involuntary flexion and extension of the fingers, toes, arms and legs. The patient stated that the movements

had diminished somewhat during the month prior to admission. Rapid facial contour changes were noted. Diminution of these movements was noted at rest. The speech was noted to be staccato-like and the handwriting was described by the patient as becoming less legible during the first month of illness.

Patient developed marked dyspnea and coughing about 9:30 P.M. on August 14, 1948. Examination revealed a pulse of 130, marked apprehension, marked dyspea and orthopnea. Patient was given M.S. grains 1/6 and positive pressure oxygen with some relief of her symptoms. At 3:00 A.M. August 15, 1948, the patient again became extremely cyanotic and irrational. The lungs were filled with crepitant rales. Pulse and blood pressure were unobtainable. Patient expired at 4:00 A.M.

Dr. A. E. Kanter, Obstetrician:

I have some added information on this patient, as she was a patient of mine. I saw the patient for the first time on April 4th, about 8 weeks after her last menstrual period with approximate due date on November 17th. At that time examination showed no unusual findings: blood pressure of 110/60 and a slight suggestion of a presystolic thrill. Outside of the usual childhood diseases, history failed to reveal any serious trouble; she had had whooping cough, measles but no scarlet fever. Appendectomy was done at the age of 16. Also on two subsequent visits she did not present any unusual conditions. However, on the third visit it was obvious that she had some dis-

LABORATORY FINDINGS

BloodCount:	RBC	Hb.	WBC	Stabs	Segs	Eos	Lymphs	Mono.
8/11/48	3.7 Mill.	66.6	11,600	4	80	2	10	4
Blood Chemistry	Sugar	Urea N.	Inorg. Phosphorus		Calcium		Cholesterol	
8/12/48	96	9.4	4.4		8.7		287	
"	CO₂ Combining power		Chlorides					
	57		600					

Urinalysis:	Sp. Gr.	React.	Alb.	Sugar	WBC	RBC	Casts	
8/12/48	1,025	Acid	Tr.	0	10-15	5-10	0	

8/12/48—Sed. Rate: 50

8/12/48—Hematocrit: 39

8/11/48—Serologic test for syphilis: Negative.

turbance, particularly as to speech and coordination, with a rise of the pulse rate to 110. She did have a bad family history: her mother, her sister and her grandmother had attacks of hyperthyroidism. Therefore the first thing that I thought of in this particular patient was thyroid pathology. I had her admitted to the hospital on the 4th of June—2½ months after the first time I had seen her. At that time she had a normal sedimentation rate, no albuminuria, a white count of 7,400, and her temperature never exceeded 98.9°. Under phenobarbital alone, all her purposeless movements disappeared. For that reason I suspected that these were choreiform movements accompanying pregnancy. With a basal metabolism of 24, which is not unusual in pregnancy, she was discharged. I saw her several times after that; she was perfectly all right, had no choreiform movements whatever, showed the usual gain of weight. No albuminuria or glycosuria occurred and her blood pressure remained normal.

The subsequent events apparently occurred between the last time I saw the patient and the time she was admitted to the hospital. I did not know that while she was under my observation she had a bronchitis. She went to an internist who gave her some cough medicine which gave her a good deal of relief because she did not complain of it when she came to see me. The patient's brother thought she needed a rest and took her to Michigan City. From that time on her troubles began. I know that she consulted a physician there who could not find anything essentially wrong with her except the bronchitis, which he considered as on an asthmatic basis. Since I left for a vacation at that time, I have no first hand information on the further events.

Dr. C. Berkowitz, Internist:

This case is very interesting. It also shows that if we had not been able to obtain a post-mortem permission we probably would never have suspected a number of things which, I believe, the pathologist has found. The patient stressed to me more than even to the other men the fact that her trouble started with a cough

which developed around the second month of pregnancy. A week before I saw her she had gone to Michigan City and there she had an attack of dyspnea. A doctor was called in, told her she had an attack of asthma, treated her accordingly with adrenalin, and she was relieved. When I saw her on August 11th, the chief findings were: (1) extreme dyspnea, orthopnea, and tachypnea, associated with dry hacking cough. This made it almost impossible for the patient to talk and the history was secured from an aunt. (2) There were marked choreiform and athetoid movements of the arms, legs, face and trunk, which became exaggerated when called to the patient's attention. Upon questioning the patient dated these choreiform movements to the second month of pregnancy. When I saw her she was in the sixth month. (3) Her lungs were full of crepitant rales, scattered bilaterally, perhaps a little more marked on the left side. (4) There was extreme tachycardia, ranging from 128 to 140, without any apparent cardiac enlargement or other objective findings, and without any history of any rheumatic infection in childhood. No joint affection, no chorea, no rheumatic heart disease, and no frequent sore throats had ever been noted. Fluoroscopy showed extensive infiltration—or congestion—of both lungs, more marked on the left side, extending from the hilum to the periphery.

On account of this condition and the poor appearance of the patient, I urged and obtained immediate hospitalization. In trying to arrive at a diagnosis which would fit the entire picture, my impression was that of an acute bronchitis, with associated occasional asthmatic attacks causing extreme dyspnea and precipitating an alkalosis; this, I thought, aggravated the respiratory distress, caused tachypnea and tachycardia, and produced peculiar muscular twitching. These were not exactly like chorea. One day later I made a note that the laboratory findings had failed to confirm my suspicion, entertained in the presumptive diagnosis. I then considered the possibility whether toxemia of pregnancy might produce such choreiform movements.

The X-ray of the chest was repeated and showed a very peculiar picture. There was a large density in the left lung just lateral to the aorta, about 3-5 cm. in size, and both lungs showed extensive peripheral infiltrations. The picture suggested one of several possibilities: a virus pneumonia, a pneumonitis, or a metastatic malignancy, possible lymphosarcoma. The patient was afebrile throughout the three days in the hospital. Her choreiform movements, under phenobarbital, were much less marked but still present. Auscultation disclosed only a few crepitant rales at the left base. Her general appearance showed marked improvement. On the following day the patient had a rather sudden pulmonary death at 4 a.m.

The following important points were secured from the husband: the choreiform movements had developed one month after she became pregnant, although she had had some peculiar twitchings of the hand even before pregnancy. The bronchitis developed during the second month of pregnancy. In view of the absence of cardiac findings, except for tachycardia, and in view of the lack of history of joint involvement or other previous rheumatic manifestations, I felt unable to offer any additional diagnostic statements.

Dr. B. Pearlman, Internist:

I would like to make a suggestion. In 4 or 5 per cent of patients with rheumatic heart disease, mitral stenosis and insufficiency may occur without any auscultatory findings at all. I would therefore suggest that in a young pregnant woman of 23, with unexplained marked dyspnea, orthopnea, and cough, congestive failure secondary to a rheumatic heart with mitral involvement is a strong possibility.

Dr. H. N. Kamin, Cardiologist:

The electrocardiogram showed a picture of sinus tachycardia with a right heart strain pattern. This is compatible with rheumatic heart disease (rheumatic mitral stenosis) but could also appear in any condition giving rise to increased pulmonary tension.

Dr. J. Arendt, Radiologist:

The radiological study of the chest was based on one film taken 4-5 days before death. There was, at that time, far-spread involvement, but densities which were located at different levels were superimposed and appeared as confluent. The densities were most marked in the central parts in and around the hilum and they thinned out towards the periphery, leaving the apices almost clear. Our first impression was pneumonitis; the possibility of rheumatic pneumonitis was seriously considered. The differential diagnosis was edema of the lung, and it has been pointed out by Banting from Yale University that rheumatic pneumonitis has an X-ray picture which resembles pulmonary edema, characteristically as in our case leaving the apices clear. The heart appeared as of normal size and shape; no valvular involvement could be noted on our film.

The possibility of a lymphoblastoma also had to be discussed as there was visible in the left hilum a large round glandular shadow, yet the mediastinum was not widened, and there was no sign of glands elsewhere.

Dr. I. Davidsohn, Pathologist:

AUTOPSY. The heart weighed 300 Gm. which is about normal for a person of this size and age. There was some enlargement of the right ventricle, which participated in the formation of the apex. The pericardial sac contained about 40 cc. of clear straw colored fluid, each pleural cavity contained 800 cc., and the abdominal cavity about 100 cc. of similar fluid. There was no edema of the skin. The left auricle was markedly dilated and hypertrophied. The mitral valve showed two types of lesions: (1) the leaflets were shortened, thickened and hardened and the chordae tendineae showed similar changes; this was an old lesion leading to a so-called fibroplastic deformity of the valve. (2) In addition, the margins of the leaflets, especially the posterior, showed on the auricular surface recent verrucous vegetations, evidence of a recurrent endocarditis of the mitral valve, superimposed on the old fibroplastic deformity (Fig. 1). The old lesion led to a stenosis of the ostium and insufficiency of the valve. The aortic valve showed no old lesions, only a few recent verrucous vegetations. No changes were

found in the pulmonary and tricuspid valves.

Microscopic examination of the mitral valve showed the characteristic fibrinoid swelling of the deep connective tissue, some fibrinous deposits on the surface, no bacterial deposits, all of that adding up to a typical recent rheumatic verrucca. On closer examination with high-power magnification, histiocytic cells were found proliferating in the deeper layers, in addition to swelling and edema, and the surface presented fibrinous deposits. Microscopic sections were taken from various parts of the myocardium. They showed acute edema, marked fibrosis characteristic of old lesions, and occasional accumulations of cells which were arranged similar to Aschoff bodies, but the morphology of the cells was not that seen in Aschoff bodies. In other words, no typical rheumatic granuloma was found but in many places there were earmarks of an old rheumatic myocarditis. This is the interpretation one could give to large areas of fibrosis in the myocardium of a 23 year old woman.

The main lesion was present in the lungs, which weighed 2,000 Gm. together. The normal weight of the lungs would be about 700 Gm. The lungs were large and heavy, but showed no true consolidation of the type seen in a typical pneumonia, especially one caused by pyogenic microorganisms. The color was brown-red, the consistency rubbery, not friable. This picture is characteristic for what is recognized as rheumatic pneumonia. Microscopic sections showed a variety of lesions. In some places the lumens of the alveoli were filled with moderate numbers of endothelial cells loaded with brown blood pigment, heart failure cells. Much more striking were nodules consisting of spindle shaped cells, in the alveolar wall, protruding into the cavity (Fig. 2). On high power magnification these nodules were found lined on the surface with hypertrophied pulmonary alveolar cells. Nodules of this appearance have been described by Masson, are called by his name. and are considered by some as characteristic for rheumatic pneumonia. These lesions progress towards organization. The composing cells resemble fibroblasts. There is no unanimity of opinion regarding the true nature of these nodules. For instance, Herbut of Philadelphia claims that he has seen such lesions in bronchiectasis and tuberculosis and does not consider them as characteristic of rheumatic pneumonia but merely as the result of organization of interstitial exudate. However, others are not in agreement with him. Personally, I have seen such lesions only in rheumatic pneumonia, although I have done careful microscopic examinations of a great many lungs from a variety of conditions. Therefore, I am inclined to interpret them as characteristic of the rheumatic process. I would place them on the same level as rheumatic granulomas seen in synovial membranes and Aschoff nodules in the heart.

Another lesions seen in many sections was the presence of hyaline thrombi in capillaries and in larger arteries, especially arterioles. This lesion can be interpreted as evidence of damaged vascular endothelium with resulting thrombosis.

In some places considerable edema was present in the alveolar spaces which showed a tendency towards condensation at the periphery of the alveoli close to the alveolar wall with resulting formation of a structure resembling frames.

These so-called hyaline membranes have been described in a variety of conditions, like virus pneumonia, etc., but also have been described in cases of rheumatic pneumonia.

Another lesion was seen in branches of the pulmonary artery with marked thickening of the intima and formation of a granuloma-like nodule protruding into the lumen.

It is interesting to review the history of ideas regarding the specificity of rheumatic lesions in the lung. Historically, the earliest was the recognition of certain pleural changes as characteristic for rheumatic fever. Later on, characteristic changes were claimed to have been observed in the parenchyma of the lungs. One of these was the hyaline membranes previousely mentioned. However, after the first World War it was found that exactly the same type of hyaline membrane is present in influenzal pneumonia.

Others have observed it in the newborn and in the stillborn baby. Finally, the most recent opinion is that it actually is evidence of an increased permeability of the capillaries and that it can be produced experimentally in the animal by instilling into the pulmonary tree an albumin-rich fluid and then creating artificially an intermittent dyspnea.

The evidence in favor of the specific rheumatic nature of the Masson nodules is rather convincing.

The spleen showed hyperplasia.

Anatomic and Microscopic Diagnosis:

HEART: Old fibroplastic (rheumatic) deformity of mitral valve resulting in stenosis of mitral ostium and insufficiency of mitral valve; acute (rheumatic) verrucous endocarditis of mitral and aortic valves; hypertrophy of left auricle and right ventricle; fibrosis of myocardium. LUNGS: Rheumatic pneumonitis; hydrothorax, bilateral. LIVER, KIDNEYS:

Acute passive congestion . SPLEEN: Follicular hyperplasia; acute passive congestion. UTERUS: Pregnancy (5½ months). OVARY: Corpus luteum of pregnancy. BREAST: Hyperplasia of pregnancy.

The findings indicate that the main lesion was present in the lung. It is true that the patient died from heart failure, but the changes in the lung probably played an important part. According to recent reports in the literature, the development of a rheumatic pneumonitis usually aggravates the prognosis, and such patients as a rule die soon afterwards.

Some recent writers on the subject expressed the opinion that what we call virus pneumonia is nothing else but a transient rheumatic involvement of the lung of a mild nature.

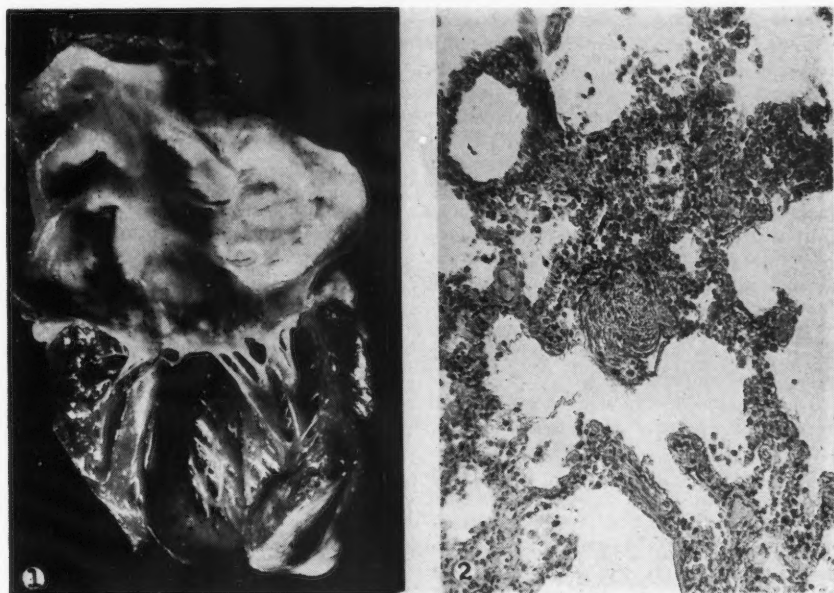The absence of Aschoff granulomas in the heart does not militate against the

Figure 1

Fig. 1. Heart. Left ventricle and left auricle. The mitral valve shows moderate thickening which involves also the chordae tendineae. In addition note the recent verrucous vegetations which extend along the line of closure of the valve.

Fig. 2. Lung. In the center of the field a representative Masson body is presented. Its location in the interalveolar septum and the fibroblasts growing into it can be visualized. Photomicrograph. X110.

diagnosis of rheumatic fever. This patient's original Aschoff granulomas probably became fibrosed long ago. The present exacerbation was probably of too short duration to lead to the formation of granulomas. Furthermore, in cases of recurrence of the rheumatic process, Aschoff bodies are not found with the same regularity as in the early acute process.

It is interesting that the fetus, which showed the development of approximately six months of pregnancy, showed no changes whatsoever, although it could be assumed that it was exposed to similar damaging influences as the mother. That does not surprise us because the lesions in the mother are interpreted as being the result of sensitization, while in the baby there was no time or opportunity for display of the same kind of mechanism as was operative in the mother.

CHILDBIRTH IS A PHYSIOLOGIC PROCESS
IRVING SIEGEL, M.D.*

The baby lay on a clean white towel. A half dozen medical students—obstetric clerks—were grouped around, awaiting their turn to pass a tracheal catheter. One student was already practicing the technique, calmly and leisurely. It wouldn't hurt the baby—it had been dead six hours. It lay still, pale and cold, a pretty boy baby, perfectly developed, full term, delivered still-born by cesarean section. A few of the students bandied jokes while awaiting their turn—an obvious attempt to cover their confusion in facing the consequences of human tragedy, probably for the first time. Several of the students had wives who were pregnant. What impression did this dead baby make on them? Could they have been thinking of the months of retching, the first quiver they felt on palpation, the anticipation of friends and family, the selection of names, and then, this. . . . And the mother of the baby, lying in her room, minus her uterus. . . . Porro cesarean. What happened? Why?

Gentlemen: Childbirth is a physiologic process. The mother was a white woman, gravida III, para II, age 38, whose previous deliveries were uneventful and resulted in two living children. Her past medical and surgical histories were negative. Her present pregnancy was uneventful until three weeks prior to term, when her blood pressure rose to 140/90 and urinalysis revealed 2+ albuminuria. She had no other symptoms. The patient was put to bed at home, given sedation and a salt-free diet. Three days later she developed severe abdominal pains fol-

* Asst. Prof. of Obstetrics, Chicago Medical School.

lowed shortly by moderate vaginal bleeding. On admission to the hospital, the patient seemed to be in moderate shock. She was pale, sweaty with anxious facies; blood pressure was 120/70, pulse 136. Examination of the abdomen revealed a term fetus, cephalic presentation, no FHT audible, uterus tense and tender. There was moderate vaginal bleeding. Diagnosis: abrupto placentae, possibly a Couvelaire uterus. Treatment: Cross-match for transfusion; double set-up. Vaginal examination revealed 2 cm. dilatation of cervix, no placenta palpable, presenting part high. A cesarean section was performed. A still-born term fetus was delivered. There were about 500 cc. of blood clots in the uterus. Examination of the uterus revealed that approximately 2/3 of the uterine wall was infiltrated with blood. The uterus did not contract down well. A hysterectomy was performed. The patient received 1000 cc. of blood.

Comment: this patient developed toxemia of pregnancy three weeks prior to term. Toxemia resulted in utero-placental apoplexy and a typical Couvelaire uterus. The fetus died from anoxemia, and, because the uterine muscle was infiltrated with blood, the uterus failed to contract after the baby was delivered. The hysterectomy was therefore performed to eliminate postpartum hemorrhage.

Conclusion: *Parturition is a normal physiological process but constant watchfulness is the price of safety.*

The last student succeeded in inserting the tracheal catheter with difficulty. He wrapped the baby in a white sheet. He pinned the sheet with safety pins.

BOOK REVIEWS

Operative Technic in General and Specialty Surgery. Written by 54 American surgeons and edited by Warren H. Cole, M.D., F.A.C.S. Cloth. Complete in 2 volumes. 1740 pages with 1700 illustrations. New York: Appleton-Century-Crofts, Inc., 1949. $30.00.

Without question, Dr. Cole's new 2 volume treatise is one of the finest works of its kind to be published within the last decade. Dr. Cole's accomplishments as a general surgeon, now recognized throughout the entire country, as well as his experience in contributing to surgical literature and in editing a textbook on general surgery, are enough guarantees of the highest standards in a text on the operative technic in specialty surgery. Of the greatest importance is the choice of contributing authors in the surgical specialties, and in this, Dr. Cole has been most successful. He has chosen recognized leaders in each field; men who are well-known for their skill as operating surgeons — surgeons who have had previous training in general surgery. This is especially evident in the chapters on the operative treatment of fractures, the neurological procedures, and in the radical surgery for carcinoma in gynecological patients.

In contrast to many other surgical texts, Cole's *Operative Technic* largely confines its descriptions to the latest accepted techniques and gives little space to descriptions of procedures that are obsolete or obsolescent. A minimum of diagnostic material is included. Dangers and precautions are clearly stated, and preoperative preparation as well as postoperative care are described in considerable detail.

Chosen for his known accomplishments and recent contributions to the technic in the various fields, each author gives in detailed fashion a clear description of the procedure he has found to be most effective for each lesion. In the chapter on thoracic surgery, precautions and pitfalls relating to the various operative procedures are discussed in a clear and arresting fashion — an excellent addition to the detailed discussion of the steps and techniques of the operations described. In the chapter on the heart and mediastinum, the surgeon with the greatest experience in this field analyzes the recent surgical advances in a part of the body that only lately has become the most intensively and dramatically explored area of surgical attack.

In addition to being most useful to experienced surgeons, this work will be invaluable for candidates for surgical "boards," for interns and residents, and for senior medical students.

Current Therapy 1950. Edited by Howard F. Conn, M.D. Cloth. 736 pages. Philadelphia and London: W. B. Saunders Company, 1950. $10.00.

This very valuable and practical text is replete with authoritative information on the latest methods for treatment of disease. The book is a record of current treatment procedures as practiced by more than 250 contributors represented. It is complete in itself and contains all the information that the busy practitioner needs in order to treat adequately the variety of disease entities and manifestations which confront him. There are many cases where two or more methods of treating a single disorder are included — this occurs when there are the usual existing variations in standard therapy. No preference, however, is indicated among such variant methods. We are certain that this volume will be *indispensible* to the general man, and it should be in all medical libraries.

Handbook of Diseases of the Skin. By Richard L. Sutton, M.D., and Richard L. Sutton, Jr., M.D. Cloth. 749 pages with 1057 illustrations. St. Louis: The C. V. Mosby Company, 1949. $12.50.

From the viewpoint of the general practitioner and medical student, this work represents a clear-cut and lucid description of all the skin pathology seen in daily practice and in hospital dispensaries. The many illustrations are well-chosen, and the pages and print are excellent. It is highly recommended to all men in the medical profession who come in contact with skin disorders, and no medical library should be without it.

Introduction to Neuropathology. By Samuel Hicks, M.D., and Shields Warren, M.D. Cloth. First edition. 494 pages with 289 illustrations. New York, Toronto, London: McGraw-Hill Book Company, Inc., 1950. $10.00.

This well-illustrated volume on the basic fundamentals of neuropathology presents an entirely new approach to the mechanisms, dynamic sequences and pathologic physiology of disease processes in nervous tissues. Devoid of out-moded neuropathological terminology, this text reflects the authors' keen interest in bringing into closer harmony the teaching of the special features of nervous disease with the basic principles of the disease processes in general pathology. This book will be of special value to the medical student and trainee in the neurologic and pathologic specialties, and should be in the medical libraries of all practicing physicians.

The Fundamentals of Bacteriology. By Joseph M. Dougherty, Ph.D., and Anthony J. Lamberti, M.S. Cloth. Second edition. 491 pages with 141 illustrations. St. Louis: The C. V. Mosby Company, 1950. $5.75.

The authors of this text have attempted to present the essentials of bacteriology and immunology to the pre-medical and medical student in a simple and direct style, and in this they have succeeded. The basic fundamentals are presented in a concise, lucid and graphic manner. In this, the second edition, the material concerning the newer antibiotics has been brought up to date, and includes descriptions of such species and drugs as bacitracin, polymidin, aureomycin, and neomycin. The section on the fungi and mycoses has been expanded and there are interesting sections on the viral, rickettsial, and potozoan diseases. The book is highly recommended to the undergraduate student as a well-written fundamental text of bacteriology, and to the medical student as a review of these fundamentals.
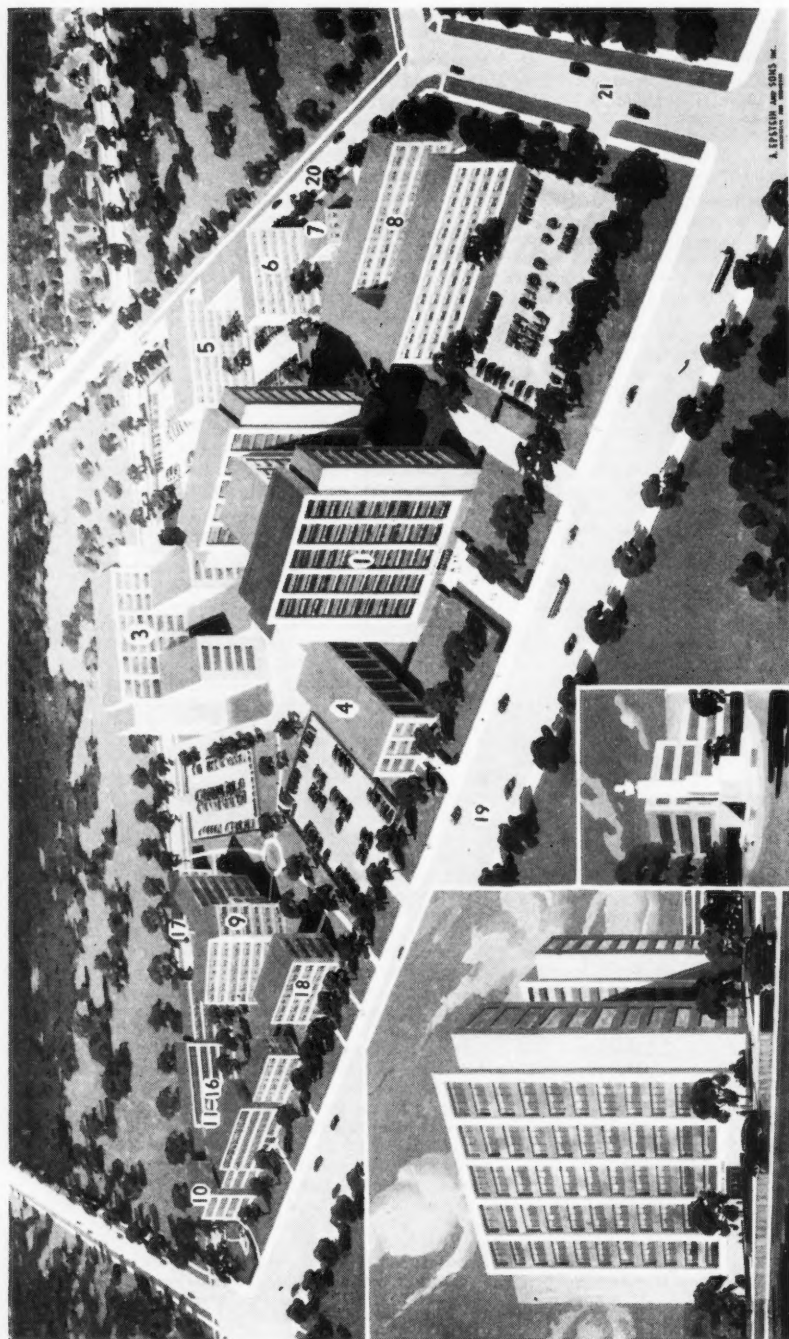
THE CHICAGO MEDICAL SCHOOL DEVELOPMENT PLAN

The site, which has been tentatively allocated by the Medical Center Commission, is bounded by West Ogden Avenue (19), South Leavitt Street, West Lexington Street (20) and Polk Street (21).

1. Chicago Medical School
2. Out-patient Clinic (not visible)
3. Hospital
4. Auditorium
5. Nurses Home
6. Administrative Staff (Apartments)
7. President's Residence
8. Students, Internes and Residents
9. Graduate School
10. Research Institute
11. Endocrine and Metabolic Research
12. Cancer Research
13. Psychiatric Research
14. Gastro-intestinal Research
15. Cardio-vascular Research
16. Full Time Teaching Staff (Apts.)
17. Geriatrics Research
18. Graduate Students

Extracted from the New York State Medical Journal (April, 1950). Report of Dr. Harold Brown, Chairman, Medical Licensure Committee.

"... Of those who had taken the examinations given by the State Department of Education, there were 1,080 who tried during 1949, of which number 386 passed and 674 failed. The total number of graduates from nine medical schools in New York State was only 85, of which 39 failed and 46 passed ... Quite revealing to me was the *Chicago Medical School* accomplishment. This was formerly a C school and now has an A rating. It had 69 graduates take the examination and 52 passed. *Percentagewise, this is the best record attained by any group.* (80 percent)."

The Chicago Medical School has been approved by the New York State Education Department.

FACULTY

Dr. Borovsky, Professor of Pediatrics, has been appointed Chief of Staff of La Rabida Hospital and is the official representative of the Chicago Medical School at the La Rabida Hospital.

Dr. Luisada, Associate Professor of Medicine and Director of the Cardiology Laboratory has recently been elected to the Chicago Society of Internal Medicine.

Dr. B. Blivaiss, Assistant Professor of Physiology and Pharmacology has been elected a member of the Society for Experimental Biology and Medicine.

Dr. Dreikurs, Professor of Psychiatry, will deliver a series of lectures entitled Cultural Upheaval and Modern Family Life under the sponsorship of the Community Child Guidance Centers.

Department of Anatomy

Dr. Edgar A. Congdon has recently completed a monograph concerning variations in the axillary artery of the Siamese. This monograph is an important contribution to the science of anatomy.

It would be difficult and impractical for the clinician concerned to learn each of these variations. Therefore, the variations could be grouped into a fewer number of major categories or, "Supertypes" by the elimination of less important distinguishing features and the rarer variations.

This attempt by Dr. Congdon is the first authoritative investigation of the variations of a variable artery.

Dr. Koenig has enrolled in a special course on the Medical Aspects of Atomic Warfare at the Argonne Laboratory of the University of Chicago.

Department of Physiological Chemistry

Dr. Richard Roberts, Dr. W. Dasler, Dr. A. Goldfarb, Mr. Teitel and Mr. Mosovitch are jointly investigating the effects of hemin derivatives containing Fe_{57} and Fe_{59} on rats having the Walker strain Carcinoma. Derivatives of hemin in liquid ammonia are being used in this study in an attempt to obtain a derivative which will be retained in different concentrations by the carcinoma and the normal tissue. This work is being done in the radiation tracer laboratory at the Chicago Medical School.

ALUMNI

The Alumni Association extends its heartfelt sympathy to the family and friends of these honored dead:

Dr. Raoul Lazzaar Vioran of Ohio, Class of 1910.
Dr. A. J. Hill of Chicago, Class of 1911.
Dr. Frank J. Norton, Class of 1918.
Dr. Frank Bautista, Class of 1926.
Dr. Jemkins H. Tomer, Class of 1932.
Dr. V. M. Trimm of Illinois, Class of 1935.

Class of 1934

Dr. Judd R. Breakstone announces the opening of offices for the practice of Gynecology and Obstetrics in Miami Beach, Florida.

Class of 1937

Dr. Irving S. Blumenfield has been appointed Resident in Medicine at the Queens General Hospital, Jamaica, New York.

Class of 1940

Dr. Irving H. Blumenfeld was elected to the office of Delegate to the New York State Medical Society for the two year period of 1948-1949, as representative of the Kings County Medical Society.

Dr. H. F. Kapov has been appointed Physician-in-Charge of the Chicago Plant of Armour and Company.

Dr. and Mrs. Frederick Spector of Brooklyn, New York announce the birth of Sandra Lee Spector on February 22, 1950.

Class of 1943

Dr. Maximilian O. Goldsmith received his license to practice medicine from the State Board in Florida.

Dr. Pat S. Vitiello was appointed Chief Surgeon of the Chicago Police Department.

Class of 1946

Dr. Leo A. Asher recently received his license to practice medicine in the state of Florida.

Dr. Benedict E. Liewen, of Belleflower, Illinois, has recently established the Liewen clinic in Belleflower.

Class of 1947

Dr. and Mrs. David N. Yatzkan announce the birth of their son, Jules S. Yatzkan.

Class of 1948

Dr. Arvin S. Glickman was granted a Postdoctoral Fellowship in the Medical Sciences at Duke University School of Medicine for a basic training course in the biological effects of ionizing radiation.

Class of 1949

Dr. and Mrs. Marshall Persky announce the arrival of Richard Jack Persky on March 26, 1950.

STUDENTS

Class of 1950

Congratulations are in order to Mr. and Mrs. Marvin L. Jaffee on their marriage on March 26, 1950 in Chicago.

Class of 1952

Congratulations are in order for Mr. and Mrs. Arnold Tobin on the birth of their first child, Joseph J. on March 22, 1950.

Best wishes also are extended to Na-

than Kaplan, whose wife is expecting their second child later in May.

Eugene Fierer will celebrate his summer vacation by marrying Miss Dianne Paris of Brooklyn.

After a five year engagement (so he claims), Seymour Metrick will make Miss Harriet Rubon, of Chicago, his bride on June 25, 1950.

A slightly more impatient sophomore, Gil Douglas, will wed Miss Joan Peters of Chicago on June 17, 1950.

Congratulations to Milton Arnold on his engagement to Sylvia Stillerman on April 24, 1950.

After a fairly rapid courtship, congratulations are in order to Irving Rosenberg and Miss Bernice Leiboff of Chicago on their recent engagement.

Class of 1953

Congratulations are in order to Max R. Waller who will marry Miss June Wolin on September 1, 1950.

ORGANIZATIONS

Phi Beta Pi

The Beta Mu chapter of Phi Beta Pi was installed into the national organization on February 4, 1950, under the direction of Dr. L. B. Arey of Northwestern University, Dr. E. J. Van Liere, the Supreme Secretary-Treasurer, Dr. E. Beeson, Professor Emeritus of Dermatology at Loyola University, and Drs. J. N. Essenberg and L. Strong of the Chicago Medical School.

Under the leadership of Vernon Phillips who has succeeded Al Modert as archon, the group looks forward to increasing participation in the activities of the school and the national organization. The active membership of nineteen has elected the following officers for the coming year: Chester Meyers, Vice-Archon; James Terrano, Secretary; Phillip Bonn, Treasurer; and Walter Kitt, Chapter Editor.

Phi Lambda Kappa

In honor of the late Dr. Maurice Oppenheim, the Alpha Rho Chapter of Phi Lambda Kappa Fraternity has established an annual Maurice Oppenheim Memorial Lectureship.

The first annual lecture was given on

Friday, May 5, 1950, at the Kling Auditorium of the Mount Sinai Hospital, Chicago. The guest lecturer was Dr. Irvine H. Page of the Cleveland Clinic Foundation, Cleveland, Ohio, renowned for his work in renal physiology. His subject was, "Arterial Hypertension — Its Nature and Treatment." Dr. Oppenheim was Professor and Chairman of the Department of Dermatology and Syphilology of the Chicago Medical School.

At a recent meeting of the fraternity new officers for the coming year were elected. Art Lisbin was elected President, Sandy Cohn, Vice-President, Stu Cohn, Secretary, Mel Pick was re-elected as Treasurer, and Izzy Siegel was elected Corresponding Secretary.

Phi Delta Epsilon

National Headquarters has granted the chapter a yearly lectureship, to be entitled the John J. Sheinin Lectureship. The first in this series is to be the opening event when the Chapter officially resumes functioning in October, after the Summer recess. The lectureship was founded to honor Dr. Sheinin, a member of Phi Delta Epsilon, for his outstanding contributions in the field of education.

Following a national Phi Delta Epsilon custom, the chapter elected its outstanding graduate for the year 1950. He is Lawrence Ravich, the first Consul, who was instrumental in founding the Chapter at this school.

New officers were elected in April to serve for a year. Of the class of 1951, Samuel Farber was elected Consul, with Perry Gross as Senior Senator and Jack Schiff as Marshal. In the class of 1952, David Schulman became Vice-Consul, Bernard Wattenmaker, Treasurer, George Ehrlich, Secretary, and Melvin Levinson the Junior Senator. Robert Langs, the Historian, and Walter Griesbach, the Assistant Treasurer, are of the class of 1953.

Assoc. of Internes and Medical Students

The AIMS National Committee on Discrimination now resides at the Chicago Medical School. The problem of discriminatory practices in Medicine against students, house staff officers, and patients always has been a major AIMS activity consonant with the stated policy "to serve ourselves, our profession, our community." It was very logical and indeed natural that the chapter at our school assume leadership in this field. Anyone interested in this work please contact the AIMS representative in your class. The service that the Committee on Discrimination can render to the medical community and to society generally depends upon the widest participation of students at this school.

Student American Medical Association

The Chicago Medical School Chapter of the Student American Medical Association was formed April 25, 1950. The objectives of this association shall be to advance the profession of medicine, to instruct and inform its members of the purposes and ideals of organized medicine, and to prepare its members to meet the social, moral and ethical obligations of the profession of medicine. This newly formed national organization is an affiliate of the American Medical Association. The Chicago Medical School Chapter has a current membership of fifty students.

EDITOR'S NOTE

It is not with little regret that I take leave of my favorite project. These 2½ years of intimate association with the QUARTERLY have been pleasant, stimulating instructive and, at times, painful and irritating. But these are the things from which understanding is born.

These thoughts I would like to leave with my successors . . . .

Verbosity and volubility are neither keys to scientific contribution nor successful publication.

Encourage, cultivate, nurture the younger men on the staff and the alumni, for they need you. And when they inherit the earth, let them inherit the QUARTERLY too.

For the most outstanding — and most unrecognized — job by a staff member during the past year my choice is Mr. Murray Rosenberg of the Features Staff.

I know that I speak for the remainder of the graduating staff when I say that wherever we are, if we can be of help, we are at your service.

It has been a pleasure.

Irwin S. Morse
Editor

CLASS OF '50

"The Board of Trustees, Faculty and Graduating Class of THE CHICAGO MEDICAL SCHOOL announce the thirty-sixth commencement Saturday morning, June 24, 1950, Chicago, Illinois."

PLACE: John B. Murphy Auditorium of the American College of Surgeons.

GUEST SPEAKER: Dr. Otto P. Kretzmann, President of Valparaiso College and member of the Board of Trustees.

THE GRADUATING CLASS

Name	Interneship
Anderson, William W.	Charity Hosp. of Louisiana, 1532 Tulane Ave., New Orleans, Louisiana
Appley, S. Noam	Kings County Hosp., 451 Clarkson Ave., Brooklyn 3, New York
Braverman, Ephraim F.	Philadelphia General Hosp., Philadelphia, Pa.
Bronsky, David	Cook County Hosp., Chicago, Ill.
Brown, Murray W.	Charity Hosp. of Louisiana, New Orleans, La.
Carey, James R.	San Diego County General Hosp., San Diego, Calif.
De Furia, Charles V.	St. Anthony De Padua Hosp., Chicago, Ill.
Ehrich, Melvin	Charity Hosp. of Louisiana, New Orleans, La.
Elegant, Lawrence D.	Michael Reese Hosp., Chicago, Ill.
Filman, Seymour J.	New York City Hosp., Welfare Island, New York
Fiorica, Anthony	St. Mary's Hosp., Rochester, New York
Fishbein, Herbert L.	Coney Island Hosp., Ocean Parkway & Ave. Z, Brooklyn, New York
Fox, Milton D.	Jersey City Medical Center Hosp., Jersey City, N. J.
Grayson, Leonard D.	U. S. Marine Hosp., Stapleton, Staten Island, N. Y.
Gordon, Leonard I.	Morrisania City Hosp., Bronx, New York
Gottleib, Reynold J.	University of Illinois Hosp., Chicago, Ill.
Greenberg, Alfred	Mt. Sinai Hosp., Chicago, Ill.
Guido, John A.	Sacred Hosp., Spokane, Wash.
Hilton, Wayne	Cedars of Lebanon Hosp., Los Angeles, Calif.
Jaffee, Marvin L.	Cook County Hosp., Chicago, Ill.
Kantor, Nathan I.	Bridgeport Hosp., Bridgeport, Conn.
Katz, David	Mt. Sinai Hosp., Chicago, Ill.
Komajda, Raymond M.	St. Anne's Hosp., Chicago, Ill.
La Rocca, Vincent J.	Los Angeles County General Hosp., Los Angeles, Cal.
Lieberman, Murray	Coney Island Hosp., Rockaway Parkway & Ave. Z, Brooklyn, New York
Litt, Jerome Z.	Kings County Hosp., Brooklyn 3, New York
Ludwig, Abraham S.	Morrisania City Hosp., Bronx, New York
Lunsky, Louis L.	Fordham Hosp., Bronx, New York
Magidson, Joshua	Grace Hospital, Detroit, Michigan
Matanky, Seymour R.	Cook County Hosp., Chicago, Ill.
Miller, Milton	Cook County Hosp., Chicago, Ill.
Modert, Alson W.	St. Joseph Hosp., Kansas City, Missouri
Moldovan, Alfred	Morrisania Hospital, Bronx, New York
Morse, Irwin S.	Charity Hosp. of Louisiana, New Orleans, La.
Moser, Lawrence	Los Angeles County Harbor Gen'l. Hosp., Torrance, Cal.
Oransky, Philip	Morrisania City Hospital, Bronx, New York
Ostrove, Robert	Kings County Hospital, Brooklyn 3, New York
Packer, Marvin S.	Cook County Hosp., Chicago, Ill.
Ravich, Lawrence	Morrisania City Hosp., Bronx, New York
Rodman, David C.	Muhlenberg Hosp., Plainfield, New Jersey
Rosenthal, Harry L.	Akron City Hospital, Akron, Ohio
Rosner, Sol	Fordham Hosp., Southern Blvd., Bronx, New York
Safadi, David	Kings County Hosp., Brooklyn 3, New York
Sandberg, Herschel	Jewish Hosp., Philadelphia, Pennsylvania
Scaramella, Michael J.	St. Elizabeth's Hosp., 1433 N. Claremont, Chicago, Ill.
Schaefer, Gerschen L.	Mt. Sinai Hosp., Chicago, Ill.
Schlansky, Seymour M.	The Jewish Hosp. of St. Louis, St. Louis, Missouri
Schwartz, William	Coney Island Hosp., Ocean Parkway & Ave. Z, Brooklyn, N. Y.
Shaw, Morton A.	Mt. Sinai Hosp., Cleveland, Ohio
Sherman, Maurice J.	Mt. Sinai Hosp., Chicago, Ill.
Silberman, Jack	Cook County Hosp., Chicago, Ill.
Solomon, Daniel	Cook County Hosp., Chicago, Ill.
Stogis, Francine	Fordham Hosp., Bronx, New York
Tartaglia, Tollio F.	Morrisania Hosp., Bronx, New York
Tucker, Alvin Z.	San Bernardino County Hosp., San Bernardino, Calif.
Vesce, Joseph P.	Metropolitan Hosp., Welfare Island, New York
Wertheim, J. Marvin	Queens General Hosp., Jamaica, Long Island, N. Y.

INDEX TO VOLUME 11

SUBJECT INDEX

AUTHOR INDEX

BOOKS REVIEWED

APPLETON-CENTURY-CROFTS, INC.—
Cole, Warren H. ...."Operative Technique in General and Specialty Surgery"
Kolmer, John A. ...."Clinical Diagnosis by Laboratory Examination"

THE BLAKISTON COMPANY—
Craige, E. Horne ...."Bensley's Practical Anatomy of the Rabbit"
Jones, H. W., et al ....Blakiston's New Gould Medical Dictionary
Smith, L. W. and Gault, E. S. ...."Essentials of Pathology"
Tobin, Charles E. ....Shearer's "Manual of Human Dissection"

F. A. DAVIS COMPANY —
Hamilton, W. F. ...."Textbook of Human Physiology"
Alpers, B. J. ...."Clinical Neurology"
Bates, W. and Judovich, B. ...."Pain Syndromes"
Miller, G. W. ....Young's "Handbook of Anatomy"

PAUL B. HOEBER COMPANY —
Barrow, D. W. ...."Clinical Management of Varicose Veins"

LEA & FEBIGER —
Brownell, K. A. and Hartman, F. A. ...."The Adrenal Gland"
Faust, E. C. ...."Human Helminthology"

J. B. LIPPINCOTT COMPANY —
Karsner, H. T. ...."Human Pathology"
Rolnick, H. C. ...."Practice of Urology"

C. V. MOSBY COMPANY —
Dougherty, J. M. and Lamberti, A. J. ...."Fundamentals of Bacteriology"
Faulkner, R. L. and Douglass, M. ...."Essentials of Obstetrical and Gynecological Pathology"
Shands, A. R. ...."Handbook of Orthopedic Surgery"

McGRAW-HILL BOOK COMPANY —
Windle, W. F. and Nonidez, J. F. ...."Textbook of Histology"
Hicks, S. ...."Introduction to Neuropathology"

W. B. SAUNDERS COMPANY —
Berens, C. ...."The Eye and Its Diseases"
Sunderman, W. F. and Boerner, F. ...."Normal Values in Clinical Medicine"
Boies, L. H. ...."Fundamentals of Otolaryngology"
Cantarow, A. and Trumper, M. ...."Clinical Biochemistry"
Christopher, F. ...."A Textbook of Surgery"
Conn, H. F. ...."Current Therapy"
Custer, P. R. ...."Atlas of the Blood and the Bone Marrow"
Duncan, G. G. ...."Diseases of Metabolism"
Friedberg, C. K. ...."Diseases of the Heart"
Fulton, J. F. ...."A Textbook of Physiology"
Levine, S. A. and Harvey, W. P. ...."Clinical Auscultation of the Heart"

WILLIAMS & WILKINS COMPANY —
Best, C. H. and Taylor, N. B. ...."The Physiological Basis of Medical Practice"
Eddy, W. H. ...."Vitaminology"
Veith, I. ...."The Yellow Emperor's Classic of Internal Medicine"
White, C. ...."Diseases of Women"

YEARBOOK PUBLISHERS, INC. —
Boas, E. P. and Boas, N. F. ...."Coronary Artery Disease"
Page, I. H. and Corcoran, A. C. ...."Arterial Hypertension"